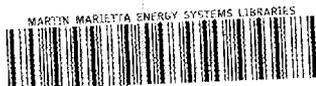


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NUREG/CR-3572 Vol. II
(ORNL/TM-8939/V2)

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MARTIN MARIETTA

Determination of Metabolic Data Appropriate for HLW Dosimetry. II. Gastrointestinal Absorption

M. Cristy
R. W. Leggett

Prepared for the
Division of Waste Management
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Under Interagency Agreement DOE 40-550-75

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NUREG/CR-3572 Vol. II
ORNL/TM-8939/V2
Dist. Category RH

Health and Safety Research Division

DETERMINATION OF METABOLIC DATA APPROPRIATE FOR HLW DOSIMETRY.
II. GASTROINTESTINAL ABSORPTION

M. Cristy and R. W. Leggett

NOTICE: This document contains information of a preliminary nature.
It is subject to revision or correction and therefore does not
represent a final report.

Date Completed - December 1985
Date Published - February 1986

Prepared for the
Division of Waste Management
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555
Under Interagency Agreement DOE 40-550-75

NRC FIN No. B0289

Prepared by the
OAK RIDGE NATIONAL LABORATORY
Oak Ridge, Tennessee 37831
operated by
MARTIN MARIETTA ENERGY SYSTEMS, INC.
for the
U.S. DEPARTMENT OF ENERGY
Contract No. DE-AC05-84OR21400



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CHAPTER 1. INTRODUCTION

This report and a previous one (Eckerman et al. 1984) evaluate the dependence on chemical forms of estimates of health effects in high-level waste (HLW). As in the previous report, it is assumed that the organ dose is a suitable index for health effects from exposure to radionuclides, and our discussion is usually directed toward the metabolism and dosimetry of various chemical forms of a radionuclide rather than toward health effects per se.

This study is needed because the chemical species of radioelements released to the environment from a high-level waste repository may not be adequately described by the metabolic and dosimetric models of Publication 30 of the International Commission on Radiological Protection (ICRP 30). Our previous report dealt with two main topics: (1) identifying those chemical forms of radionuclides which are likely to reach humans after migration from a waste repository and (2) identifying those aspects of the body's metabolism that depend upon the chemical form.

It was pointed out in the previous report that one of the greatest uncertainties now present in estimating organ doses from given environmental exposures to various chemical forms of radionuclides lies in the estimate of the fraction absorbed through the gastrointestinal tract to blood. This report deals with two topics on absorption through the gastrointestinal tract. In Chapter 2 we derive an upper bound for the absorption fraction of plutonium for adults, which is based on data from adult humans. In Chapter 3 we review the important topic of absorption of radionuclides (strontium and actinides) by neonates and juveniles and present a table of recommended absorption fractions for neonates, infants, children, and adults.

REFERENCE FOR CHAPTER 1

Eckerman, K. F., Leggett, R. W., Meyer, R., and O'Kelley, G. D. 1984. Determination of metabolic data appropriate for HLW dosimetry (ICRP-30), I. U.S. Nuclear Regulatory Commission Rep. NUREG/CR-3572 (also Oak Ridge National Laboratory Rep. ORNL/TM-8939).

CHAPTER 2. AN ESTIMATE OF THE GASTROINTESTINAL ABSORPTION
FRACTION FOR ENVIRONMENTAL PLUTONIUM IN ADULT HUMANS

INTRODUCTION

For evaluation of occupational exposures, the International Commission on Radiological Protection (ICRP) currently recommends the value 10^{-4} for the fraction f_1 of soluble plutonium absorbed from the GI tract to blood (ICRP 1979). This value is based on data derived in laboratory experiments often conducted under conditions much different from those expected in environmental exposures to plutonium. Recent results and reviews by several authors (Bair 1979; Harrison 1982; Johansson 1983; Kocher and Ryan 1983; Larsen et al. 1981; Sullivan et al. 1979; Sullivan 1980; Sullivan et al. 1980) indicate that chronic intake of low levels of environmental forms of Pu by laboratory animals may lead to observed values of f_1 substantially larger than 10^{-4} . In recent reviews, Bair (1979) and Kocher and Ryan (1983) recommended a value of 10^{-3} , and Harrison (1982) and Johansson (1983) recommended a value of 5×10^{-4} for GI uptake of environmental plutonium. The value recommended by Harrison and Johansson appears to be intended as a "most likely" value based on the animal data, while the recommendation of Bair and that of Kocher and Ryan may be intended as slightly conservative for considerations of radiation protection. In the present report an upper bound of 2×10^{-3} for f_1 is estimated from data for a group of adult humans who had ingested elevated levels of Pu in their normal diet. The value 10^{-3} may be a reasonable choice for f_1 for use in assessments of environmental exposures to plutonium, since it is in close agreement with values recommended in recent reviews, and it is only a factor of 2 below the upper bound estimated here for the group of adult humans.

DERIVATION OF AN UPPER BOUND OF THE ABSORPTION FRACTION FOR ADULT HUMANS

The diet of the Finnish Lapp population is known to contain abnormally high levels of plutonium because of the lichen-reindeer-man food chain peculiar to the region. By estimating the quantities of

plutonium ingested and inhaled by Lapps and their whole-body contents and comparing these with analogous quantities in Southern Finns, Mussalo-Rauhamaa and coworkers (1984) attempted to determine the fraction f_1 of ingested plutonium absorbed to blood. Their approach was to solve the simultaneous equations

$$a_1 X + b_1 Y = c_1 \quad (1)$$

$$a_2 X + b_2 Y = c_2 \quad (2)$$

where Eq. (1) is for Southern Finns and Eq. (2) is for Finnish Lapps, a_i is the lifetime inhalation intake of Pu, b_i is the lifetime dietary intake, c_i is the body burden at death (in 1977-79), and the unknowns X and Y are the fractional absorptions from the airways and from the gastrointestinal tract (f_1), respectively. Their estimates of a_i , b_i , and c_i were 18, 36, and 1.37 pCi, respectively, for Southern Finns and 13, 535, and 1.40 pCi, respectively, for Lapps. An estimate of 9.0×10^{-4} was obtained for Y (f_1) after a slight adjustment for the fraction of activity assumed to be excreted. The authors noted some problems with this approach, but it does nonetheless yield a valuable preliminary result since it is the only available estimate of f_1 for plutonium that is based on data for humans.

The main difficulty with this approach is that the solution for Y will vary substantially as estimates of the body burden and the inhalation intake vary within their ranges of uncertainty. In fact, since autopsy data do not establish a clear difference between the whole-body burdens of the two groups or between their lung burdens, one cannot use this method to rule out the value $f_1=Y=0$, obtained if $a_1=a_2$ and $c_1=c_2$. Although the estimate of 9×10^{-4} agrees well with current estimates based on data for non-humans, one must question whether the agreement is fortuitous in view of the uncertainties in the coefficients in Eqs. (1) and (2). In the following it is shown that, despite the uncertainties involved, the data and general approach of Mussalo-Rauhamaa and coworkers may be used to obtain a reasonably reliable estimate for an upper bound of the GI absorption fraction for environmental plutonium. This upper bound is only a factor of 2 higher than their estimate for f_1 .

The largest error associated with an estimate of the whole-body burden of Pu based on autopsy data generally arises from the non-uniformity of Pu in the skeleton. Mussalo-Rauhamaa and coworkers used rib samples to estimate skeletal burdens. Various results indicate that the concentration of Pu in rib may be higher than average for the skeleton, but it is probably not lower than average (Mussalo-Rauhamaa et al. 1979). Whatever the direction of error, this should be considered a systematic error and thus should apply equally to Lapps and Southern Finns. We are seeking a smallest reasonable upper bound for f_1 , and, as can be shown, the estimate of this value obtained from the approach used here will change in proportion to systematic adjustments in estimated whole-body burdens. Thus, skeletal burdens estimated by Mussalo-Rauhamaa and coworkers should not be adjusted since their error, if any, would probably be on the high side.

Autopsy data for five adult male Lapps are listed by Mussalo-Rauhamaa and coworkers (1984). The maximum estimated body burden of these subjects (three reindeer herders, a fisherman, and a farmer) is 1.56 pCi. Because of the relatively small sample of Lapps considered, this value is adopted here as a conservatively high estimate of the whole-body burden of a typical adult male Lapp. The average whole-body burden of 1.37 pCi determined for adult male Southern Finns is based on a relatively large number of samples and will be adopted for this analysis.

The estimated dietary intake of Pu for the Lapps during the period 1954-1978 is 535 pCi (Mussalo-Rauhamaa et al. 1984). There is no way to determine whether this is representative of the sample population's intake, but it should be assumed that some error is involved. Since the upper-bound estimate will increase as the assumed Pu intake by the sample population decreases, it will be assumed conservatively that this estimate is 50% higher than the real value, which would then be about 360 pCi. The relatively small dietary intake for Southern Finns has little effect on the final estimate of f_1 when allowed to vary within a reasonable range; the original estimate by Mussalo-Rauhamaa and coworkers (1984) of 36 pCi is used here.

The inhalation intake for the entire lifetime of the Lapps and Southern Finns was based on the estimated air concentration of Pu in northern and southern Finland, respectively, and a breathing rate of 20 m³/day (Mussalo-Rauhamaa et al. 1984). It was noted that the breathing rates of the Lapps may not be the same as those of typical Southern Finns, since the Lapps are generally outdoor workers. The amount of plutonium inhaled by Lapps was estimated as 13 pCi, compared with 18 pCi for Southern Finns, with the difference arising from the fact that the average concentration of Pu in surface air in the Lapp region was estimated to be only 72% of the concentration in southern Finland. It is assumed here that the inhalation intake by Southern Finns is $k_1 Q$ and that of Lapps is $k_2(0.72Q)$, where k_i denotes the appropriate breathing rate in each case and Q is the integrated concentration of plutonium in surface air in southern Finland. The following equations may then be used to obtain an upper bound for f_1 , without having to assign a numerical value to the breathing rate:

$$k_1 QX + 36Y = 1.37 \quad (3)$$

$$0.72k_2 QX + 360Y = 1.56. \quad (4)$$

From Eq. (4) we know that $Y < 0.0043$. Substituting this into Eq. (3) yields $X > 1.22/k_1 Q$, and putting this back into Eq. (4) gives $Y < 0.0043 - 0.0024k_2/k_1$. There are two reasons why one might suspect that $k_2 > k_1$: the Lapps may perform heavier work than Finns, as an average; and the limited autopsy data did not show a lower concentration of Pu in lungs of Lapps than in lungs of Southern Finns, despite the lower air concentrations experienced by the Lapps. An upper bound for Y can be found by assuming $k_2 = k_1$; this gives $Y = f_1 < 0.0019$. An iteration of the procedure described in this paragraph yields $f_1 < 0.0017$, and allowance for the small amount of plutonium lost from the body (ICRP 1979) between 1954 and 1978 would raise this upper bound to about 0.002.

A slightly more detailed description of this work appeared in Health Physics (Leggett 1985).

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CHAPTER 3. GASTROINTESTINAL ABSORPTION OF RADIONUCLIDES BY YOUNG ANIMALS
AND THE DEVELOPMENT OF THE G.I. TRACT AS IT RELATES TO THIS PROBLEM

INTRODUCTION

Absorption of several radionuclides present in high-level waste (plutonium, americium, and neptunium) has been shown to be higher in neonates than in adults of various species by factors of 10-1000. Less information is available on absorption in juvenile animals after weaning and before sexual maturity, especially in animals that have a protracted juvenile period similar to that of humans. Except for strontium, no direct information on absorption by human infants and children of radionuclides present in high-level waste is available. Most of the information on absorption by neonates is from one animal model, the rat, but increased absorption by neonates does seem to be a general phenomenon -- other rodents (hamster, guinea pig) and mammals of other orders (swine, sheep, cow, dog) show increased absorption of plutonium, for example.

In fact, neonates seem to absorb metals in general more than do adults -- this is true for nutritional metals such as iron and calcium and toxic, non-nutritional metals such as lead and cadmium (Table 1). The reasons for this general increased absorption are not completely clear. Many workers have suggested that the high rate of pinocytosis by the epithelial cells of the villi in the small intestine that occurs in some species in the immediate postnatal period (and is associated with absorption of immunoglobulins and other macromolecules) is the mechanism or one of the mechanisms involved. However, the evidence is better for some metals than others, and there may be species differences (Henning and Leeper 1984). Neonatal guinea pigs do not absorb immunoglobulins postnatally, although they do take up macromolecules into the intestinal cells by pinocytosis for the first 1-2 days of life (Clarke and Hardy 1970; Lecce and Broughton 1973); Sullivan (1980b) reported that guinea pigs 0.5-1 days old show increased absorption of plutonium, and Harrison (1985) recently found that neonatal guinea pigs older than 2 days, where pinocytotic uptake has ceased, also show increased absorption. Lead is

Table 1. Metals that are reported to be absorbed by young mammals more readily than by adults.

Metal	Species	References
<i>Actinides</i>		
Th	Rat	Sullivan (1980b); Sullivan, Miller, and Ryan (1983a)
Pa	Rat	Sullivan, Miller, and Ryan (1983a)
U	Rat	Sullivan (1980b)
	Swine	Sullivan and Gorham (1982)
Np	Rat	Sullivan (1980b); Sullivan, Miller, and Ryan (1983b); Sullivan, Ruemmler, and Ryan (1984)
	Hamster	Harrison and David (1984)
	Swine	Sullivan and Gorham (1982)
Pu	Rat	Ballou (1958); Mahlum and Sikov (1967); Finkel and Kisielewski (1976); Sullivan (1980b); Sullivan and Gorham (1982); Sullivan, Miller, and Ryan (1983b); Sullivan, Miller, and Goebel (1984); Sullivan et al. (1985b)
	Hamster	Harrison and David (1984)
	Guinea pig	Sullivan (1980b)
	Swine	Buldakov (1968); Sullivan (1979); Sullivan (1980b); Sullivan and Gorham (1982); Sullivan, Miller, and Goebel (1984)
	Cattle	Sutton et al. (1977)
	Dog	Buldakov et al. (1970); Sullivan and Gorham (1982)
Am	Rat	Moskalev et al. (1973); Sullivan (1980b); Sullivan et al. (1985b)
	Hamster	Harrison and David (1984)
	Swine	Sullivan and Gorham (1982)
Cm	Rat	Semenov et al. (1973); Sullivan (1980b); Sullivan et al. (1985b)
	Swine	Sullivan and Gorham (1982)
Cf	Rat	Sullivan (1980b)
Es	Rat	Sullivan (1980b)
<i>Lanthanides</i>		
Ce	Rat	Inabe and Lengemann (1972); Shiraishi and Ichikawa (1972); Eisele et al. (1980)
	Mouse	Matsusaka et al. (1969); Naharin et al. (1969, 1974); Matsusaka (1971); Feige et al. (1973); Eisele et al. (1980)
	Swine	Mraz and Eisele (1977c); Eisele et al. (1980)
Pm	Rat	Sullivan, Miller, and Goebel (1984)
	Swine	Sullivan, Miller, and Goebel (1984)

**Table 1. Metals that are reported to be absorbed by young mammals more readily than by adults.
(Continued).**

Metal	Species	References
<i>Group 2a</i>		
Ca	Rat	Hansard and Crowder (1957); Taylor et al. (1962); Ghishan et al. (1980)
	Cattle	Hansard et al. (1954)
	Human	Harrison (1959)
Sr	Rat	Taylor et al. (1962); Forbes and Reina (1972)
Ba	Rat	Taylor et al. (1962)
Ra	Rat	Taylor et al. (1962)
<i>Group 4a</i>		
Sn	Rat	Sullivan, Miller, and Goebel (1984)
Pb	Rat	Kostial et al. (1971,1978); Forbes and Reina (1972); Henning and Leeper (1984)
	Mouse	Keller and Doherty (1980a,b)
	Monkey	Willes et al. (1977); Pounds et al. (1978)
	Human	Alexander et al. (1974); Ziegler et al. (1978)
<i>Transition elements</i>		
Cr	Rat	Sullivan, Miller, and Goebel (1984)
Mn	Rat	Kostial et al. (1978); Kirchgessner et al. (1981)
	Cattle	Carter et al. (1974)
Fe	Rat	Taylor (1962); Ezekiel (1967); Loh and Kaldor (1971); Forbes and Reina (1972)
	Human	Darby et al. (1947); Schulz and Smith (1958); Garby and Sjolín (1959); Gorten et al. (1963)
Co	Rat	Taylor (1962)
Cu	Rat	Mistilis and Mearrick (1969)
	Sheep	Suttle (1975)
Zn	Rat	Ballou (1960); Kirchgessner et al. (1981); Sullivan, Miller, and Goebel (1984)
Nb	Rat	Mraz and Eisele (1977a)
	Swine	Mraz and Eisele (1977b)
	Sheep	Mraz and Eisele (1977b)
Tc	Rat	Sullivan, Miller, and Goebel (1984)
Ru	Mouse	Matsusaka et al. (1969); Matsusaka (1971)
Cd	Rat	Kello and Kostial (1977a,b); Kostial et al. (1978,1979); Sasser and Jarboe (1977)
	Mouse	Matsusaka (1972)
	Guinea pig	Sasser and Jarboe (1979)
	Swine	Sasser and Jarboe (1980); Sullivan, Miller, and Goebel (1984)
Hg	Rat	Kostial et al. (1978,1979); Walsh (1982)

one of the best characterized metals. In neonatal mice, lead is absorbed primarily in the ileum (distal small intestine), by pinocytosis, but lead is also absorbed in the jejunum (just proximal to the ileum) by a different, but unknown, mechanism (Keller and Doherty 1980a). In neonatal rats, lead is absorbed primarily in the duodenum (extreme proximal small intestine), where pinocytosis is unimportant. In the ileum, lead is taken up by the intestinal wall, probably by pinocytosis, but little of this is absorbed into the general circulation. Most of this lead is eventually returned to the contents of the intestine, by sloughing of senescent epithelial cells, and eliminated with the feces (Henning and Leeper 1984).

The increased retention of metals in the wall of the neonatal small intestine may be important for radiation protection, since metal radionuclides may irradiate cells in the intestinal wall, including the radiosensitive crypt cells, for longer periods. Several actinides have been shown to be retained tenaciously in the intestinal wall of neonatal rats and swine (Sullivan 1980b; Sullivan and Gorham 1982).

Absorption of metals by neonates appears to be a process with at least two steps: (1) uptake of the metal by the epithelial cell and (2) transfer from the epithelial cell to the general circulation. When uptake is by pinocytosis, differences among metals are probably smaller than when by other mechanisms. Greater differences among metals are seen with transfer to blood or lymph; and for radiation protection, these differences are important both for irradiation of tissues distant from the intestine and for irradiation of cells in the intestinal wall. In addition, some metals may be absorbed in part by routes other than through the epithelial cells, but these routes are not well characterized (see Sweeting, 1984). Damage to the intestinal epithelium, as occurs in diseases such as coeliac sprue, may lead to changes in absorption (Walker 1981). The mechanisms of absorption of heavy metals by adult animals, either via the epithelial cells or other routes, are also not well known.

How this information on rats and other mammals may be extrapolated to the human infant and child, for the purpose of estimating gut absorption factors for radiation protection, is problematical. How important pinocytosis is for absorption by human infants is not clear,

although it appears that infants do absorb macromolecules to a greater extent than do adults (Walker and Isselbacher 1974; Walker 1981). The time period over which the greatly increased absorption seen in neonates of other species may occur in infants is also not clear -- it may occur for only a few days or weeks, or it may occur until weaning from a milk diet. For protection of the public from environmental contamination leading to contamination of food and water, Harrison (1982; 1983a,b) has proposed increased gut absorption factors for plutonium, americium, curium, and neptunium that apply to the first year of life (Table 12). For all chemical forms of plutonium other than the insoluble oxides and hydroxide, he recommends an average value of 1% be applied to the first three months, when the infant is assumed to be on a milk diet; and absorption is then assumed to decline linearly during the weaning period to 0.05% (his recommended adult value) at nine months of age and remain at 0.05% thereafter. (The ICRP (1979) recommends 0.01% for workers.) For an average value to apply to the entire first year of life, he recommends 0.5%. For the insoluble oxides and hydroxide of plutonium, he recommends that average values of 0.1% and 0.05% absorption be used for the first three months and first year, respectively, and the ICRP (1979) value of 0.001% be used after nine months of age. For all chemical forms of americium and curium, he recommends that average values of 1% and 0.5% absorption be used for the first three months and first year, respectively, and the ICRP (1979) value of 0.05% be used after nine months of age. For all chemical forms of neptunium, he recommends that average values of 1% and 0.5% absorption be used for the first three months and first year, respectively, and 0.1% be used after nine months of age -- note that this latter value, which is 1/10 that recommended by the ICRP (1980) for workers, is based largely on data published after the ICRP made its recommendations. Harrison (1983a, p. 30) states that in "evaluating the enhancement in the absorption of the actinides in newborn animals, extrapolation of the available animal data to absorption in the human is particularly tenuous." We agree with this statement and agree that his proposed values are reasonable estimates, given current knowledge. The National Radiological Protection Board of the U.K. has adopted these recommended values for protection of the public (NRPB 1984).

For adults we recommend a slightly more conservative estimate of absorption of soluble forms of plutonium (0.1% vs 0.05%), based on the arguments in Chapter 2. We also recommend this value for all forms of americium and curium in the environment (see Table 12).

These estimates will need to be reviewed periodically as the mechanisms of absorption of actinides in particular and in heavy metals in general become better understood. These estimates are probably conservative, except perhaps for children older than nine months. The question whether children older than nine months absorb actinides and other radionuclides more readily than do adults has not been adequately addressed in radiation protection. Children appear to absorb several times more iron and lead than do adults (Gorten et al. 1963; Ziegler et al. 1978), but whether this holds true for actinides and other metals is unknown. We suggest that assuming absorption of actinides by children older than nine months is 2-3 times that in adults (see Table 12) would be prudent until this question has been tested in an animal with a protracted juvenile period similar to that in humans (it may be necessary to use a primate model).

Strontium follows calcium pathways closely, and it is often used as a marker for calcium in intestinal absorption studies (Gmaj and Murer 1984). Strontium absorption is nearly 100% in suckling rats, declines to about 25% in weaned juveniles and to about 10% in adults (Taylor et al. 1962). Human infants one month to one year old absorb about 25% of strontium in their normal diets, as measured in metabolic balance studies, which is within the range of absorption of 10-35% reported for adults (Kahn et al. 1969). Kahn et al. also reported that percentage calcium absorption is similar in infants and adults (about 40%), but Harrison (1959) reached a different conclusion, based on metabolic balance studies with human subjects with high calcium intakes. The infants in these studies absorbed 40-50% of the calcium, whereas children 3-5 years old and adults absorbed less than 20%. Premature infants absorbed about 70%.

We have concluded that absorption of strontium by infants is probably between one and two times that by adults, and the amount of dietary calcium may affect the percentage absorbed. Absorption by neonates may approach 100%.

DEVELOPMENT OF THE G.I. TRACT

The epithelium of the small intestine of mammals is immature at birth, and the relative maturity varies widely from species to species. There are a number of structures, enzymes, and processes that change (mature) during the first few days, weeks, or months after birth (Koldovsky 1969). We shall focus on the process of pinocytosis (or endocytosis), which is associated with the uptake of immunoglobulins and other macromolecules, because it has been suggested by many authors that the high absorption of metals may be via that mechanism. However, it should be cautioned that there are many other differences between the immature and mature intestine, many less well understood than pinocytosis, that may affect absorption of metals; and for some metals in some species, there is evidence for high absorption independent of pinocytosis.

Uptake and Transport of Macromolecules by the Intestine

Newborn mammals become immunized to certain pathogens passively by receiving maternal immunoglobulins either prenatally, postnatally, or both, depending upon species (Table 2). Prenatally immunoglobulins are passed from the maternal circulation through the yolk-sac or placental membranes, and postnatally they are passed from colostrum or milk through the intestinal epithelium. Guinea pigs, rabbits, and man receive immunity prenatally; rats, mice, cats, and dogs receive immunity both prenatally and postnatally; ruminants, swine, and horses receive immunity only postnatally. The colostrum of those species in which transmission of immunity occurs after birth is characterized by its high content of immunoglobulins, in contrast to those in which such transmission does not occur; when transmission continues for a long period after birth the milk also has a high immunoglobulin content, but when transmission is confined to a brief neonatal period the initial high colostrum content falls very rapidly to a low level in the milk (Brambell 1970). The major immunoglobulin in these species is IgG antibodies, the predominant immunoglobulin in serum. In human colostrum and milk most of the immunoglobulin is IgA antibodies, which are

Table 2. Time and route of passive immunity in mammals (Class Mammalia) (after Brambeil, 1970).

Infraclass	Classification		Prenatal		Postnatal		
	Order	Species	Route	Transmission	Route	Transmission	
Metatheria	Marsupialia	Wallaby	None	0	Gut	+++ (180d)	
Eutheria	Insectivora	Hedgehog	Unknown	+	Gut	++ (40d)	
		Rodentia ^a	Rat	Yolk-sac	+	Gut	++ (20d)
		Mouse	Yolk-sac?	+	Gut	++ (16d)	
		Guinea pig	Yolk-sac	+++	None	0	
	Lagomorpha	Rabbit	Yolk-sac	+++	None	0	
	Artiodactyla ^b	Swine		None	0	Gut	+++ (24-36h)
			Cattle, goat, sheep	None	0	Gut	+++ (24h)
	Perissodactyla	Horse	None	0	Gut	+++ (24h)	
	Carnivora	Cat, dog	Unknown	+	Gut	++ (1-2d)	
	Primates	Monkey, human	Placenta	+++	None	0	

^aThe guinea pig is in a different suborder from that of rats and mice.

^bCattle, goats, and sheep are all in the family Bovidae of the suborder Ruminantia (ruminants). Swine are in a different suborder.

hypothesized to combat enteric pathogens in the lumen of the neonatal gut.

The process by which γ -globulins and other macromolecules are taken up by the immature epithelium of the small intestine and transported to the blood or lymph circulation is shown in Figure 1. Material is engulfed by membrane of the microvilli and this membrane pinches off to form vesicles (phagosomes) containing the macromolecules. These phagosomes migrate to the supranuclear region of the cell, where the vesicles coalesce with lysosomes to form large vacuoles called phagolysosomes. Within these structures intracellular digestion may occur, and smaller molecules may pass through the vesicular membrane into the cytoplasm of the cell, where it may be then transported to the circulation in the normal way. Those particles which escape digestion are extruded into the intercellular space by reverse endocytosis (exocytosis).

In animals such as ruminants and swine, in which absorption of macromolecules is limited to a short period after birth (24-36 h), there is an intense and nonselective uptake and transport (Figure 2, right). A wide variety of macromolecules such as albumins, globulins, insulin, enzymes, and the synthetic molecule polyvinylpyrrolidone (PVP) have been shown to be taken up and transported (see Lecce and Broughton, 1973).

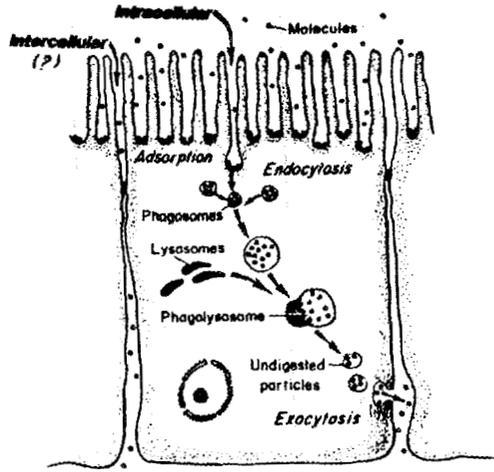


Figure 1. General mechanisms for the uptake and transport of macromolecules by the intestine. **Intracellular uptake:** After adsorption and endocytosis by the microvillous membrane, macromolecules are transported in small vesicles and larger phagosomes. Intracellular digestion occurs when lysosomes combine to form phagolysosomes. Intact molecules that remain after digestion are deposited in the intercellular space by a reverse endocytosis (exocytosis). **Intercellular uptake:** Alternatively, macromolecules may cross the "tight junction" barrier between cells and diffuse into the intercellular space. (Figure and caption from Walker, 1981.)

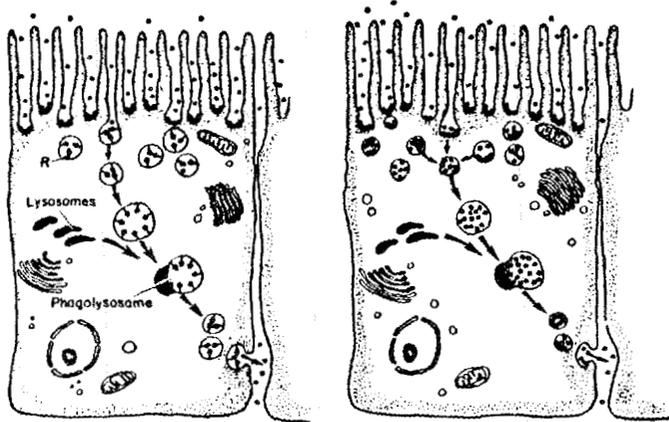


Figure 2. Mechanisms of macromolecular absorption in the neonatal mammalian intestine. **Left:** Selective transport of maternal γ -globulins in colostrum occurs in the jejunum of newborn rats via a specific receptor site (R) present on the microvillous membrane. γ -Globulins are presumed to be protected from intracellular lysosomal digestion because of attachment to the receptor site and are transported in large quantities out of the cell. **Right:** A nonselective uptake and transport of other macromolecules occurs throughout the small intestine of most neonatal animals. Immature intestinal absorptive cells engulf large quantities of macromolecules. After intracellular digestion in phagolysosomes, very small quantities are deposited in the intercellular space. (Figure and caption from Walker, 1981.)

In rats and mice, which have a prolonged period of absorption of macromolecules after birth (16-20 days), there is a selective absorption of γ -globulins (Figure 2, left). Other large molecules are taken into the epithelial cells by pinocytosis, but γ -globulin is transported selectively. It has been hypothesized that the γ -globulin binds to receptors within the vesicles and this protects it from digestion.

Closure

It is important to distinguish between the processes of uptake or internalization of macromolecules into the epithelial cells and the subsequent transport into the blood or lymph. The phenomenon of "closure" has been variously defined as the cessation of absorption of macromolecules or the cessation of uptake, and these two processes do not necessarily occur at the same time (Lecce and Broughton 1973). For example, the guinea pig, like man, does not absorb macromolecules after birth (Table 2) and its intestine is said to be closed at birth under the former definition. However, its intestinal epithelium does take up macromolecules by pinocytosis for 1-2 days after birth (Clarke and Hardy 1970; Lecce and Broughton 1973), and its intestine is said to be closed at 1-2 days of age under the latter definition. The rabbit, which also receives passive immunity prenatally only, can take up macromolecules until about 23 days of age (Clarke and Hardy 1970; Lecce and Broughton 1973). In the swine, which receives passive immunity after birth, the entire small intestine except the proximal duodenum can both take up and transport macromolecules during the first 24-36 h of life. After this time the ability to transport is lost, but the epithelium can still take up macromolecules by pinocytosis until about 18-20 days of age. Starting at the time the ability to transport ceases, there is also a gradual loss of the ability to internalize macromolecules -- the proximal small intestine loses this function first and the loss proceeds distally toward the ileum, which is the last to lose the function (Lecce 1973). In rats and mice, cells in the jejunum and ileum take up macromolecules nonselectively (Clark 1959; Clarke and Hardy 1969; Solari et al. 1984), but only in the jejunal cells is there selective transport of γ -globulin (Rodewald 1970, 1973; Mackenzie 1972). This distinction

between uptake and transport may be important in absorption of metals. For example, we may speculate that in cells where material is taken up by pinocytosis but transport of macromolecules is absent, a metal could still be absorbed into the circulation by passing through the vacuolar membrane with digestive breakdown products and then passing through the cell membrane; alternatively, the metal could be tightly bound to material that does not pass out of the vacuole or cell and be excreted after the senescent cell is sloughed into the intestinal lumen.

Application to Man

Lecce and Broughton (1973) have hypothesized that nonselective uptake of macromolecules is a general phenomenon in immature mammalian intestinal epithelium. They speculate that this process also occurs in human neonates from the following evidence: pinocytotic processes have been seen in electron micrographs of human fetal intestine; neonates fed cow's milk may develop circulating antibodies to cow's milk proteins or they may develop an allergy to these proteins, which suggests that small amounts of these proteins were absorbed. Others have reported that a larger percentage of infants under 3 months of age have serum samples containing antibodies to food antigens than do those exposed to antigen after 3 months, which suggests that food proteins are absorbed into the circulation more readily during the first three months of life than later on (see Walker, 1981). What effect this may have on absorption of metals is unknown, but it suggests that human neonates could also show enhanced absorption.

ABSORPTION OF METAL RADIONUCLIDES AND SELECTED OTHER METALS

The absorption by young mammals of plutonium, americium, neptunium, and strontium -- radionuclides present in high-level waste -- is reviewed here. Because curium is similar to americium in many properties, it is also included, and the sparse data on other actinides is reviewed briefly. Although the mechanisms of absorption of metals in general is beyond the scope of this review, the work on several metals other than those found in high-level wastes gives useful insights. Thus

the absorption of iron and lead by young mammals will be reviewed briefly. Iron is of interest because Pu(IV) and, to a lesser extent, Am(III) and Cm(III) have some physical and chemical similarities to Fe(III). Absorption of iron and lead is elevated (compared with adults) long after the neonatal period in children, and this raises questions about possible increased absorption of other metals in children during the period from infancy to adulthood. Experiments on absorption of lead in the neonatal rat and mouse intestine yield insights on mechanisms and sites of absorption that may or may not apply to other metals.

Plutonium, Americium, and Curium

An excellent review of the absorption of plutonium, americium, and curium by adult and neonatal mammals has been published by Harrison (1982,1983a), and his recommended values for absorption of these radionuclides by infants, children, and adults have been adopted by the National Radiological Protection Board of the U.K. (NRPB 1984). Our Tables 3-5 and 7-9 are similar to his tables but are arranged differently to highlight certain relationships (as far as possible, the tables are arranged by chemical form, species, and age, in that order); some additional information is included in our tables, and recently published results have been added.

Plutonium

Data on the absorption of the nitrate, the citrate complex, and "biologically incorporated" forms of plutonium by young mammals are given in Tables 3-5. Data on the more insoluble oxides are given in Table 7. No data are available for absorption by infants or children, but there are data for a variety of species -- rats, hamsters, guinea pigs, swine, cattle, and dogs -- especially in the immediate postnatal period.

The most striking aspect of the data is that, for the soluble forms, absorption is very much higher in neonatal animals than in adults (Tables 3-5). Retention of plutonium in the intestinal wall and contents is also much higher and longer lasting than in adults (the

Table 3. Absorption of plutonium nitrate by young rats.

Isotope and oxidation state	Dose		Number of animals	Age (days)	Total % retained ^a	% retained in intestine		Reference			
	Mass	Activity				Wall	Contents				
239	100µg	6µCi	≥5	1	0.25			Ballou (1958)			
				2	0.18						
				7	0.10						
				10-13	0.11						
				21	0.019						
				33	0.002						
				39	0.003						
				45	0.002						
				56	0.013						
238(IV)	0.0021µg	0.037µCi	2	4h	5.1	47	28	Sullivan (1980b)			
				0.023	0.39	3	4h		4.7	27	24
				0.24	4.1	3	4h		5.9	1.6	6.1
				0.0021	0.037	1	1		2.9	61	30
				0.023	0.39	3	1		1.6	32	28
				0.24	4.1	3	1		2.4	1.3	6.8
238(IV)	3.5µg/kg	60µCi/kg	3	1	1.6	34	26	Sullivan (1980b)			
238	2.9µg/kg	50µCi/kg	3	1	1.8	40	26	Sullivan and Gorham (1982)			
238	0.2µg	3µCi	11	1	2.8			Sullivan and Gorham (1982)			
239(VI)	32µg	2.0µCi	4	1	1.4	11	11	Sullivan (1980b)			
237(IV)	0.000004	0.05	3	2	2.8	40	11				
238(IV)	0.12	2.0	7	2	2.2	0.75	0.55	Sullivan (1980b)			
238(VI)	0.12	2.0	17	2	3.6	9.5	1.7				
239(IV)	32	2.0	5	2	0.4	4.6	3.0				
239(VI)	32	2.0	8	2	0.7	4.7	3.6	Sullivan and Gorham (1982)			
237	0.0003µg/kg	3.7µCi/kg	9	2	1.7						
239	3900	240	9	2	0.3						
237/239	0.6µg/kg	0.9µCi/kg	6	2	2.4	(67) ^b		Sullivan, Miller, and Ryan (1983b)			
239	1900	120	10	2	1.0	(36) ^b					
238	13µg/kg	230µCi/kg	8	2	2.3 ^c	(4.2) ^b		Sullivan et al. (1985b)			
239	2040	130	10	2	0.9	(23) ^b					
241(IV)	0.02µg	2.8µCi	6	3	1.6	46	27	Sullivan (1980b)			
238	13µg/kg	220µCi/kg	13	4	3.0			Sullivan and Gorham (1982)			

^aAmount retained in body, except GI tract, at 21 days (Ballou) or 7 days (all others) after administration. Results by Sullivan, Miller, and Ryan also exclude skin.

^bWall and contents combined.

^cThis experiment is apparently identical with one reported in Sullivan, Miller, and Goebel (1984).

Table 4. Absorption of plutonium nitrate by young of species other than the rat.

Species	Isotope and oxidation state	Dose		Number of animals	Age (days)	Interval between gavage and necropsy (days)	Total % retained ^a	% retained in intestine		Reference
		Mass	Activity					Wail	Contents	
Guinea pig	238	5µg/kg	90µCi/kg	2	0.5	3.5	3.3	8.1	9	Sullivan (1980b)
				2	1	3	2.3	0.8	23	
Dog	238	2.6µg/kg	45µCi/kg	5	2	7	6	1.2	8.3	Sullivan and Gorham (1982)
Dog	239			≥2	3	1	0.14 ^b	up to 66		Buldakov et al. (1970)
Swine	238	23µg/kg	400µCi/kg	2	2h	36h ^c	47	32 ^d	0.8 ^d	Sullivan (1979)
Swine	238	1.5µg/kg	25µCi/kg	1	0.5	3.5	31 ^e			Sullivan (1980b)
				1	0.5	7.5	30 ^e	4		
				2	0.5	12.5	26 ^e	1.4	0.08	
				2	0.5	21.5	29 ^e	0.8	0.002	
				2	1	10	42 ^f	27		
				2	1	9	79 ^f	15	9	
Swine	238	1.2µg/kg	20µCi/kg	2	1	7	13	25	36	Sullivan and Gorham (1982)
Swine	239(IV)	380µg	24µCi	2	1	7	11	43	7.4	Sullivan and Gorham (1982)
				2	1	7	16	51	6.3	
				2	1	21	11			
				2	1	21	17			
Swine	238	~1µg/kg	15-20µCi/kg	3	1	7	18 ^g	61 ^g		Sullivan and Gorham (1982)
Swine	238	0.9µg	15µCi	3	1	2-4	15	64 ^g		Sullivan and Gorham (1982)
Swine	238	3.8µg	65µCi	3	2	7	22	37 ^h		Sullivan, Miller, and Goebel (1984)
Swine	238	0.8µg/kg	14µCi/kg	2	5	7	7.4			Sullivan and Gorham (1982)
Swine	238	0.8µg/kg	14µCi/kg	2	5	7	12	54	11	Sullivan and Gorham (1982)
				2	10	7	5.4	42	15	
				4	14	7	1.9	6.5 ⁱ	25	
				4	14	7	1.9	6.5 ⁱ	25	
				3	21	7	0.3	0.05 ⁱ	0.3	

^aAmount retained in body, except GI tract, at various times after administration. Values of Sullivan and co-workers for dog and swine, except the one labelled with footnote a, also exclude skin.

^bAmount retained in skeleton and liver. An additional 1% was retained in the remaining carcass (artefact?).

^cLesser amounts were retained at 6, 12, and 24h, in part due to substantial retention in contents of stomach, but retention in stomach was only 3% at 36h.

^dSmall intestine only. Retention in large intestine wall and contents was 5%.

^eFed synthetic diet after birth.

^fNursed by sow.

^gNot clear whether this includes the contents also.

^hSmall intestine only.

ⁱSmall intestine only. Retention in small intestine wall of the 5- and 10-day-old swine in this experiment was 51 and 40%, respectively.

Table 5. Absorption of citrate complexes and "biologically incorporated" forms of plutonium by young mammals.

Species	Isotope and chemical form	Dose		Number of animals	Age (days)	Interval between gavage and necropsy (days)	Total % retained or absorbed ^a	Reference	
		Mass	Activity						
Rat	239 citrate			3	1	4h ^b	0.46	Mahlum and Sikov (1967)	
				3	20		0.14		
				3	21		0.10		
				3	35		0.16		
Rat	237/239 citrate	0.6µg/kg	0.9µCi/kg	11	2	7	1.8	Sullivan, Miller, and Ryan (1983b)	
		1900	120	7	2		2.8		
Rat	238 citrate	11µg/kg	200µCi/kg	8	2	7	2.2	Sullivan et al. (1985b)	
		2040	130	7	2		1.7		
Rat	238 citrate	10µg/kg	170µCi/kg	6	7	7	3.3	Sullivan et al. (1985b)	
		238 citrate added to liver	8.4	140	6		7		2.3
		238 incorporated in liver	5.7	95	6		7		1.9
Rat	239 citrate	80ng	5.0nCi	6	7-16	2-11	2.0 ^c	Finkel and Kisielecki (1976)	
		180	11	11	27-36		0.08 ^c		
		340	21	10	46-55		0 ^c		
		290	18	10	76-85		0 ^c		
		370	23	10	245-254		0 ^c		
	239 incorporated in goat milk	38	2.4	11	7-16	3.2 ^c			
		85	5.3	12	27-36	0.24 ^c			
		130	8.4	10	62-71	0.3 ^c			
		180	11	10	230-239	0 ^c			
Hamster	239 citrate	0.3µg	0.02µCi	5	1		3.5	Harrison and David (1984)	
		0.3	0.02	6	4	1.4			
		0.7	0.04	9	7	0.02			
		3	0.2	6	22	0.007			
		7	0.4	6	30	0.003			
Dog	239 citrate			≥2	3	1	0.7 ^d	Buldakov et al. (1970)	
Swine	239 citrate	530µg	33µCi	3	75 ^e	1	0.19	Buldakov (1968)	
Cattle	239 citrate added to cow milk	4µg/kg/d	0.3µCi/kg/d	3	4-7 to 10-13	2-8	0.49 ^f	Sutton et al. (1977)	
		239 incorporated in cow milk		4	7-8 to 13-14		0.50 ^f		

^aAmount retained in body, except GI tract and skin. Results of Mahlum and Sikov include skin. Results of Harrison and David are by a different method, wherein retention in certain tissues is compared with retention after injection of Pu citrate and thus is an estimate of absorption.

^bApproximately the same amount was retained after 6 days for the 1- and 20-day old rats, but only half as much for the 21- and 35-day olds.

^cAmount retained 2 days after last dose. Animals were administered Pu for 10 successive days.

^d0.7% was retained in skeleton and liver; 5% was retained in the remaining carcass (artefact?).

^eStill suckling.

^fAmount retained 2 days after last dose. Animals were administered Pu for 7 successive days.

longer presence in the contents is probably due to sloughing of senescent epithelial cells that have retained plutonium tenaciously); this phenomenon could have important consequences on radiation doses to the radiosensitive crypt cells of the intestinal epithelium.

Effect of species. Rats, hamsters, guinea pigs, and dogs absorb as much as 3-6% of soluble forms of plutonium administered by stomach tube in the first few hours or days of life, which is about 100 times more than is absorbed by adults of these species. Cattle 1-2 weeks old absorbed 0.5% of plutonium administered over a seven-day period; no data on absorption by calves younger than this are available. Swine absorb 10-80% during the first several days of life, about 10,000 times more than the 0.001-0.003% reported to be absorbed by adults. (This figure for the adult is based on the nitrate, and absorption of the citrate complex and other organic forms may be higher in adults; nevertheless, absorption by neonatal swine is very much higher than by other species; see Harrison's review for data on absorption by adults.) Swine and other species of the Order Artiodactyla absorb large quantities of immunoglobulins during the first 24-36 hours of life (Table 2). The extremely large percentage of plutonium absorbed by swine may be related to this phenomenon and probably has no relevance to human absorption. However, among the species that absorb 3-6% of soluble plutonium compounds neonatal rats, hamsters, and dogs absorb moderate amounts of immunoglobulins while neonatal guinea pigs absorb no immunoglobulins (Table 2). (Although guinea pigs absorb no immunoglobulins postnatally, uptake of macromolecules into the intestinal cells by pinocytosis does occur for 1-2 days after birth (Clarke and Hardy 1970; Lecce and Broughton 1973). Sullivan's (1980b) work was with guinea pigs 0.5-1 days old, but recently Harrison (1985) has found that guinea pigs older than 2 days absorb plutonium at a similarly high rate.) Absorption of plutonium by other species that absorb no immunoglobulins postnatally (primates, rabbits) has not been tested.

Effect of age. This extremely high absorption lasts for only a very short period. Sullivan (1980b) reported that in rats absorption of ^{239}Pu nitrate decreased from 5-6% at age four hours to 2-3% at one day. Ballou (1958) reported that in rats absorption of ^{239}Pu nitrate decreased

steadily from 0.25% at age one day to 0.18, 0.10, 0.11, 0.02, and 0.002-0.004% at ages 2, 7, 10-13, 21 (age of weaning), and 33-84 days, respectively; the latter are similar to adult values measured by him (the lower absorption at age one day found by Ballou may result from the higher masses of plutonium that he administered -- see discussion of mass effects below). Mahlum and Sikov (1967) reported that 0.46% of ^{239}Pu citrate was absorbed by rats one day old (mass intubated not reported), whereas rats 20-35 days old absorbed 0.10-0.16%. Finkel and Kisielewski (1976) reported that absorption by rats of ^{239}Pu as the citrate complex or in goat milk was very much lower after weaning (see Table 5).

Hamsters are also weaned at about three weeks of age, but uptake of macromolecules by pinocytosis ceases at about 5 days of age (Lecce and Broughton 1973). Absorption of ^{239}Pu citrate declined from 3.5% at age one day to 1.4, 0.02, 0.007, and 0.003% at ages 4, 7, 22, and 30 days, respectively (Harrison and David 1984) -- note the 70-fold decline between 4 and 7 days of age. In swine absorption of immunoglobulins and other macromolecules occurs only during the first 24-36 h after birth (Table 2); loss in pinocytotic uptake, however, occurs gradually -- it begins at the duodenum at 24-36 h and proceeds caudally toward the ileum as the piglet ages to about 3 weeks (Lecce 1973). Absorption of ^{239}Pu nitrate declined from 12% at age five days to 5.4, 1.9, and 0.3% at ages 10, 14, and 21 days, respectively; absorption after weaning (6-8 weeks) was not measured (Sullivan and Gorham 1982).

Effect of mass. For adult mammals there are conflicting results on the effect of mass or concentration of plutonium administered. Sullivan reports that a smaller percentage of plutonium is absorbed when high masses are given, but other workers report no differences over wide ranges (see Harrison, 1983a). Sullivan has reported that several experiments on the absorption of plutonium nitrate in neonatal rats four hours to two days old also show a mass effect; furthermore, the percentage of plutonium retained tenaciously in the intestinal wall and contents is affected by mass administered (see Table 3, results of Sullivan, 1980b; Sullivan and Gorham, 1982; and Sullivan, Miller, and Ryan, 1983b). The results from these experiments and others listed in

Table 3 that pertain to one- or two-day-old rats are combined and plotted in Figure 3. The percentage of plutonium absorbed was fairly uniform from doses of about 10^{-4} to 10^0 $\mu\text{g}/\text{kg}$ and fell to lower values above 10^3 $\mu\text{g}/\text{kg}$. The percentage retained in the intestinal wall and contents one week after administration was 45-90% from 10^{-4} to 10^0 $\mu\text{g}/\text{kg}$ and fell to lower values above 10^3 $\mu\text{g}/\text{kg}$. For the purpose of assessing radiation doses to the public from environmental contamination, the higher values of absorption and retention at the lower masses are of interest.

Effect of chemical form. Adult mammals absorb substantially more plutonium citrate than nitrate and other inorganic forms, probably because the citrate complex is hydrolyzed less readily in the intestine (Harrison 1983a). Sullivan and co-workers have reported four experiments with neonatal rats that test the absorption of citrate vs nitrate forms, and they are collected in Table 6 and arranged by mass of plutonium dose administered. At high doses (2040 and 1875 $\mu\text{g}/\text{kg}$) the data suggest that more of the citrate form is absorbed, but it is not conclusive: at 2040 $\mu\text{g}/\text{kg}$ the citrate absorption was about twice that of nitrate absorption, but the difference is not statistically significant; at 1875 $\mu\text{g}/\text{kg}$ the citrate absorption is about three times that of nitrate absorption, and the difference is at the borderline of significance ($p \approx 0.05$) when tested with a t-test modified to take into account the highly significant difference in the variances in the two samples (Sokal and Rohlf 1960, p. 374). At the dose of 11-13 $\mu\text{g}/\text{kg}$, absorption of the two forms was virtually identical; at the dose of 0.6 $\mu\text{g}/\text{kg}$, absorption of the nitrate form was slightly higher (2.4 vs 1.8%), but the difference is again at the borderline of significance. There were no significant differences between the citrate and nitrate forms at any dose level in the amount of plutonium retained in the intestinal wall and contents seven days after administration.

Two experiments have been performed to test the effect of biological incorporation of plutonium in milk (see Table 5). Calves 4-8 days old at the start of an experiment absorbed 0.5% of ^{239}Pu administered over a seven-day period when given either as the citrate complex added to cow's milk or incorporated in cow's milk (Sutton et al. 1977). Rats seven days old at the start of an experiment absorbed 2.0%

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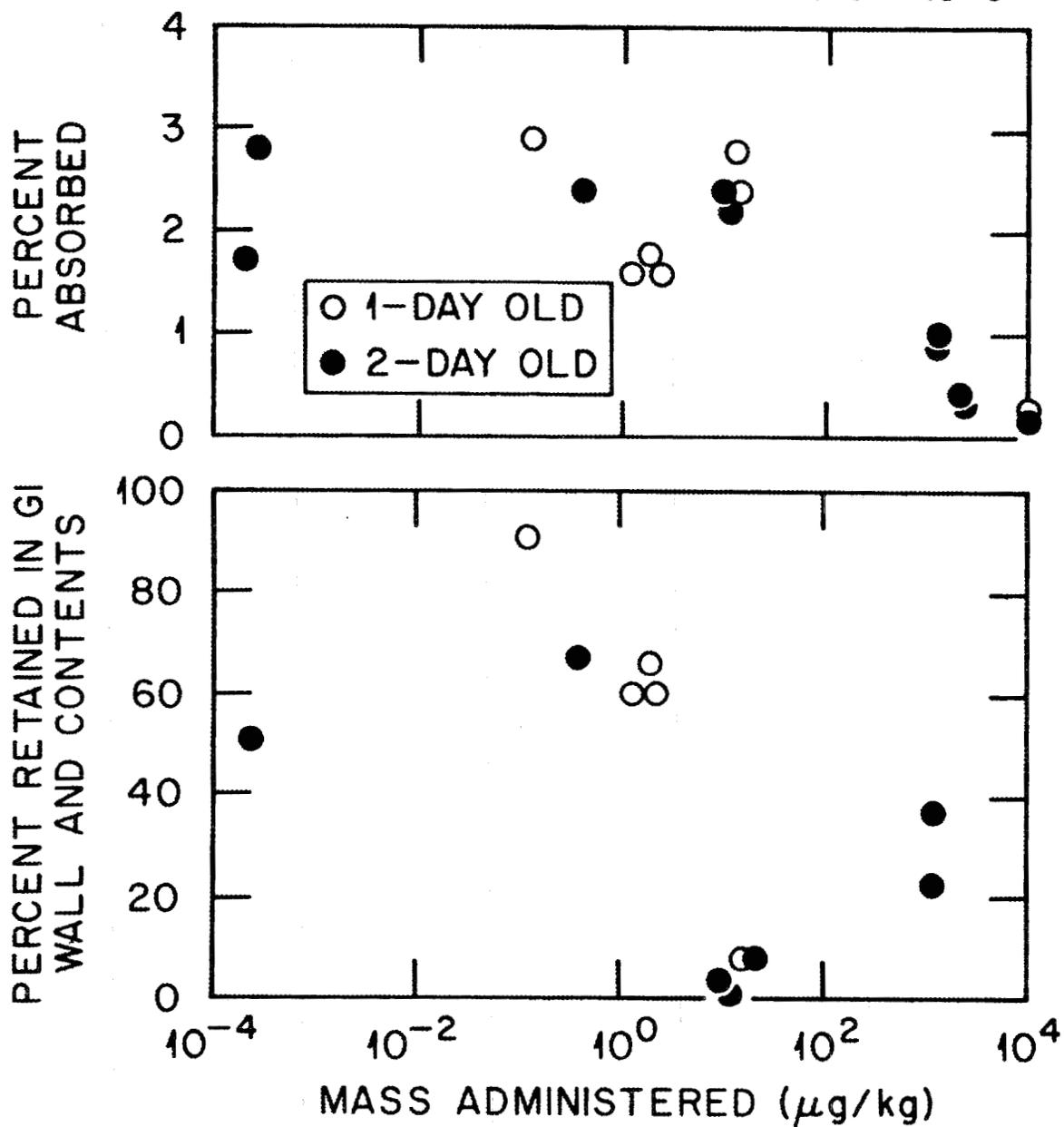


Figure 3. Amount of plutonium nitrate absorbed (**above**) or retained in wall and contents of GI tract seven days after administration (**below**) in one- and two-day-old rats. Amounts are given as percentages of gavaged dose. Plutonium was administered as a single dose. Results for the 4h-old rats and for Pu(VI) are omitted because of demonstrated age effects between four hours and one day and demonstrated effects of oxidation state.

Table 6. Absorption of nitrate vs citrate forms of plutonium in two-day-old rats.^a

Isotope Chemical form	²³⁹ Pu				²³⁸ Pu		^{237/239} Pu	
	Nitrate	Citrate	Nitrate	Citrate	Nitrate	Citrate	Nitrate	Citrate
Dose ($\mu\text{g}/\text{kg}$)	2040	2040	1875	1875	13	11	0.6	0.6
Dose ($\mu\text{Ci}/\text{kg}$)	125	125	115	115	230	200	0.9	0.9
No. of animals	10	7	10	7	8	8	6	11
% absorbed ^b	0.9 \pm 0.1	1.7 \pm 0.8	1.0 \pm 0.1	2.8 \pm 0.8	2.3 \pm 0.2	2.2 \pm 0.1	2.4 \pm 0.3	1.8 \pm 0.1
% retained in GI tract ^c	22.5 \pm 2.6	25.0 \pm 3.6	36 \pm 3	27 \pm 6	4.2 \pm 1.5	4.4 \pm 0.8	67 \pm 1	62 \pm 2

^aResults of Sullivan, Miller, and Ryan (1983b) and Sullivan et al. (1985b).

^bMean \pm standard error of the mean.

^cIn wall plus contents seven days after gavage.

of ²³⁹Pu citrate given over a ten-day period, and they absorbed 3.2% of ²³⁹Pu incorporated in goat's milk; rats of age 27 days absorbed 0.08% and 0.24%, respectively (Finkel and Kisielecki 1976). However, the citrate was apparently not given with milk, which complicates the interpretation of this experiment, and the statistical significance of these differences was not stated. Thus there is no good evidence that biological incorporation into milk increases absorption over that of the citrate complex, and the experiment with calves suggests that it does not.

The effect of biological incorporation into liver has been tested by Sullivan et al. (1985b). Seven-day-old rats were gavaged with either ²³⁸Pu citrate, ²³⁸Pu citrate added to liver, or ²³⁸Pu biologically incorporated in rat liver and suspended in a 5% citrate solution. The amounts absorbed were 3.3 \pm 0.3%, 2.3 \pm 0.2%, and 1.9 \pm 0.1%, respectively; the amounts retained in the intestinal wall and contents seven days after gavage were 3.3 \pm 3.5%, 52 \pm 6%, and 55 \pm 3%, respectively (mean \pm S.E.M.; six animals in each group). There appears to be no effect of biological incorporation, but some effect of the liver meal, especially in retention in the intestine.

Thus for protection of the public from environmental contamination at low levels, it should be assumed that in the neonatal period there are no differences in absorption among relatively soluble inorganic forms such as nitrates, organic complexes such as citrates, or biologically incorporated plutonium.

Reported absorption of plutonium oxides by adult mammals ranges from 0.000003% to 0.02%; the wide range is probably indicative of a wide range in the solubility of the oxide preparations (Harrison 1983a). Two-day-old rats absorbed 0.01-0.07% of plutonium oxide in various forms; one-day-old swine absorbed 0.04-0.2%; and one-day-old dogs absorbed 0.5% (Table 7). These values are higher than for adults, but they are considerably lower than the amounts of soluble plutonium compounds absorbed by neonates. Retention within the intestinal wall and contents is also very much less for the more insoluble oxides of plutonium (Table 7).

Effect of oxidation state. In adult mammals "under normal non-fasting conditions the absorption of plutonium is independent of the valence state in which it is ingested probably because the higher oxidation states are reduced in the acid conditions of the stomach" (Harrison 1983a, p. 26). Plutonium nitrate is absorbed by two-day-old rats and one-day-old swine about 40-70% more when given in the hexavalent state than in the tetravalent state (Sullivan 1980b; Sullivan and Gorham 1982). The rats were given 0.12 μg of ^{238}Pu nitrate or 32 μg of ^{239}Pu nitrate in each oxidation state. At the lower mass 2.2% of the Pu(IV) and 3.6% of the Pu(VI) were absorbed; and at the higher mass 0.4% and 0.7% were absorbed. At the lower mass 0.8% of the Pu(IV) administered was retained in the intestinal wall after seven days, whereas 9.5% of the Pu(VI) was so retained. At the higher mass, however, about 5% was retained for each oxidation state. The swine were given 380 μg of ^{239}Pu (IV) or 270 μg of ^{239}Pu (VI) nitrate; 11% of the Pu(IV) and 16% of the Pu(VI) were absorbed. About 25% of the plutonium was retained after seven days in the wall of the small intestine, and about 20% was retained in the wall of the large intestine, independent of oxidation state.

Harrison (1983a, p. 30) suggests that it is "possible that, while Pu(VI) is reduced in the acid medium of the adult stomach, this does not occur in the milder conditions of the neonatal gut." The acid-producing cells in the stomach of neonates of some species are not well developed during the time that immunoglobulins are absorbed (Koldovsky 1969, pp. 98-100). He also points out that the effect of oxidation state on absorption is small compared with the overall increase in absorption in neonates.

Table 7. Absorption of plutonium oxides by young mammals.

Species	Isotope and chemical form	Dose		Number of animals	Age (days)	Total % retained ^a	% retained in intestine		Reference
		Mass	Activity				Wall	Contents	
Rat	238 polydispersed 2.8 μ m GMD ^b	0.17 μ g	2.9 μ Ci	10	2	0.068	1.0	0.5	Sullivan (1980b)
	238 monodispersed 0.2 μ m GMD	0.06	1.0	8	2	0.031	0.3	0.06	
	238 monodispersed 0.9 μ m GMD	0.20	3.5	12	2	0.008	0.2	0.08	
	239 polydispersed	64	4.0	10	2	0.016	0.03	0.06	
	239 weapons grade, polydispersed	58	3.6	11	3	0.023	0.4	0.1	
Rat	238	18 μ g/kg	300 μ Ci/kg	10	2	0.05	0.07 ^c		Sullivan and Gorham (1982)
Rat	238 polydispersed, aged in water 5 days	22 μ g/kg	370 μ Ci/kg	10	2	0.038	(0.46) ^d		Sullivan et al. (1985b)
	238 supernatant from PuO ₂ -lung homogenate	1.3	22	11	1	0.060	(1.1) ^d		
Dog	238	4.7 μ g/kg	80 μ Ci/kg	2	1	0.51	0.02	0.01	Sullivan and Gorham (1982)
Swine	238	2.2 μ g/kg	38 μ Ci/kg	6	1	0.17	1.3	2.5	Sullivan and Gorham (1982)
	239	910	56	4	1	0.044	0.4	1.3	

^aAmount retained in body, except GI tract, after 7 days, except last item (9 days).

^bGMD = geometric mean diameter.

^cNot clear whether this includes the contents also.

^dDescribed as "GI Content," but probably wall plus contents.

Recommended absorption values. For the purpose of radiation protection from environmental contamination by all chemical forms of plutonium other than the insoluble oxides and hydroxide, Harrison (1983a) recommends that an average value of 1% absorption be applied to infants 0-3 months of age who are fed exclusively with a milk diet. He recommends that absorption be assumed to decline steadily during weaning from 3-9 months, and that absorption be assumed to be 0.05% after 9 months. (The 0.05% is his recommended value for adults; the ICRP (1979) recommends 0.01% for workers.) For an average value to apply to the entire first year of life, he recommends 0.5%. For the oxides and hydroxide, he recommends average values of 0.1% and 0.05% absorption be applied to the first three months and first year of life, respectively, and a value of 0.001% be applied to children after 9 months of age. (The 0.001% is his recommended value for adults and is the same as that recommended by the ICRP (1979) for workers.) These values have been adopted by the National Radiological Protection Board of the U.K. (NRPB 1984).

Harrison (1983a, p. 30) states that in "evaluating the enhancement in the absorption in newborn animals, extrapolation of the available animal data to uptake in the human is particularly tenuous" and that "neither the duration nor the extent of the enhanced absorption can be predicted with certainty." He further states that "absorption is likely to be declining rapidly in the immediate post-natal period," suggesting that his values for absorption of the actinides for the first three months and first year of life may be conservative. We agree with these statements and agree that his recommended values for plutonium and the other actinides (Harrison 1983a,b; NRPB 1984) are reasonable, given current knowledge. However, we question the assumption that children from nine months of age to adulthood absorb actinides no more readily than do adults. Children past infancy appear to absorb several times more iron and lead than do adults (see sections on iron and lead, pp. 46-56). Whether children also absorb more of the actinides is unknown, and it has not been tested adequately in laboratory animals nor in an animal which has a protracted juvenile period similar to that in humans. Additional work comparing absorption of actinides by growing, juvenile animals after weaning with absorption by adults would be useful; but this question might need to be tested also in a primate model.

Our recommended absorption values for plutonium (Table 12) are similar to Harrison's, except that our value for absorption of soluble forms by adults is slightly more conservative (0.1% vs 0.05%), based on arguments given in Chapter 2; and we recommend an absorption value for children older than nine months that is twice that for adults.

Americium and Curium

Americium and curium have not been investigated as extensively as has plutonium. The effect of chemical form has not been studied systematically, but the data suggest that in neonates there are no large differences in absorption due to chemical form (Tables 8-9).

One- and two-day-old rats and one-day-old hamsters absorbed 5-6% of americium nitrate and citrate, and one-day-old swine absorbed 2% of americium nitrate (Sullivan 1980b; Sullivan et al. 1985b; Harrison and David 1984; Sullivan and Gorham 1982). One-day-old rats absorbed 0.3% of americium oxide (Sullivan 1980b). In hamsters absorption of americium nitrate declined from 4.5% at age 1 day to 1.7, 0.5, 0.006, and 0.02% at ages 4, 7, 22, and 30 days, respectively (Harrison and David 1984).

Two-day-old rats absorbed 2-3% of curium nitrate and citrate, and one-day-old swine absorbed 6% of curium nitrate (Sullivan 1980b; Sullivan et al. 1985b). Two-day-old rats absorbed 2% of curium oxide (Sullivan and Crosby 1975; Sullivan 1980b). In rats absorption of curium chloride declined from 4% at age 7 days to 0.4% and 0.07% at ages 30 days and 6-7 months, respectively (Semenov et al. 1973).

Retention of americium and curium in the intestinal tract varied considerably from experiment to experiment, as it did with plutonium, but lack of systematic studies on mass administered or chemical form makes interpretation of these differences impossible at present. Retention in wall and contents of the intestine seven days after administration ranged from 2-26% for americium compounds and 3-25% for curium compounds.

There is no information on the site or mechanism of absorption for either americium or curium in neonates.

For the purpose of radiation protection from environmental contamination by americium or curium, Harrison (1983a) recommends that a

Table 8. Absorption of americium compounds by young mammals.

Isotope and chemical form	Species	Dose		Number of animals	Age (days)	Total % retained or absorbed ^a	% retained in intestine		Reference
		Mass	Activity				Wall	Contents	
241 nitrate	Rat	0.44 μg	1.5 μCi	8	2	4.6	15	11	Sullivan (1980b)
241 nitrate	Rat	1400 μg/kg	290 μCi/kg	9	2	5.7	(3.3) ^b		Sullivan et al. (1985b)
241 nitrate	Hamster	0.02 μg	0.07 μCi	5	1	4.5			Harrison and David (1984)
		0.08	0.3	5	4	1.7			
		0.2	0.7	5	7	0.5			
		0.3	1	6	22	0.006			
		0.1	0.3	6	30	0.02			
241 nitrate	Swine	~5 μg/kg	15-20 μCi/kg	3	1	2.1	5.3 ^c		Sullivan and Gorham (1982)
241 chloride	Rat	2 μg	8 μCi		7	0.88			Moskalev et al. (1973)
		2	8		30	0.34			
		9	30		adult	0.07			
241 citrate	Rat	1500 μg/kg	310 μCi/kg	9	2	5.9	(3.3) ^b		Sullivan et al. (1985b)
241 oxide	Rat			10	2	1.1? ^d	0.8	0.8	Sullivan and Crosby (1975)
241 oxide, polydispersed	Rat	0.6 μg	2.0 μCi	10	1	0.32 ^d	0.8	0.8	Sullivan (1980b)

^aAmount retained in body, except GI tract, after 7 days (Sullivan and co-workers) or 1-4 days (Moskalev et al.). Results of Harrison and David are by a different method, wherein retention in certain tissues is compared with retention after injection of Am and thus is an estimate of absorption.

^bDescribed as "Retained in GI Tract;" probably wall and contents combined.

^cNot clear whether this includes the contents also.

^dNumerical comparison of experimental details suggests that these two are the same experiment, in spite of the differences in reported age and percentage retained. The amount of americium in the liver and skeleton suggests that the lower value (0.32%) is the better estimate.

Table 9. Absorption of curium compounds by young mammals.

Isotope and chemical form	Species	Dose		Number of animals	Age (days)	Total % retained ^a	% retained in intestine		Reference
		Mass	Activity				Wall	Contents	
244 nitrate	Rat	0.025 μ g	2.0 μ Ci	7	2	~2 ^b			Sullivan (1980b)
		0.06	5	\geq 6	adult	0.15 ^c			
244 nitrate	Rat	3.4 μ g/kg	280 μ Ci/kg	6	2	2.9	(2.7) ^d		Sullivan et al. (1985b)
244 nitrate	Swine	~0.2 μ g/kg	15-20 μ Ci/kg	4	1	5.6	25 ^e		Sullivan & Gorham (1982)
244 chloride	Rat				7	4.0 ^f			Semenov et al. (1973)
					30	0.42 ^f			
					6-7 months	0.07 ^f			
244 citrate	Rat	3.6 μ g/kg	290 μ Ci/kg	8	2	2.8	(3.2) ^d		Sullivan et al. (1985b)
244 oxide -polydispersed, soaked 4 h	Rat	0.024 μ g	2.0 μ Ci	5	2	1.7	2.2	2.8	Sullivan & Crosby (1975); Sullivan (1980b)
				4	2	1.8	7.0	11	

^aAmount retained in body, except GI tract, after 7 days, except as noted.

^bAmount retained in liver and skeleton. This experiment was also reported in Sullivan (1974) and Sullivan & Crosby (1975), with retention reported as 6.3% and 2%, respectively. Table 10 of Harrison's review (1983a) lists this as two separate experiments, which are also mislabelled as curium oxide.

^cIncludes amount excreted in urine (0.07%).

^dDescribed as "Retained in GI Tract;" probably wall and contents combined.

^eNot clear whether this includes the contents also.

^fProtocol was not described.

value of 1% absorption be applied to infants 0-3 months of age who are fed exclusively with a milk diet, the adult value of 0.05% be applied after 9 months of age, and an averaged value of 0.5% be applied to infants 0-12 months old. These values are for all chemical forms of americium and curium, including the oxides and hydroxides. The value for adult members of the public is the same as that recommended by the ICRP for radiation workers (ICRP 1979).

Our recommendations (Table 12) are similar, except that, as for soluble forms of plutonium, we recommend 0.1% absorption for adults and 0.2% absorption for children older than nine months be used for radiation protection.

Neptunium

Absorption of neptunium compounds in young and adult mammals has been reviewed recently by Harrison (1983b), and his recommended absorption values have been adopted by the National Radiological Protection Board of the U.K. (NRPB 1984). Neptunium absorption has also been reviewed by Thompson (1982). The available data, including some results published since Harrison's review, are listed in Table 10.

It once appeared that neptunium absorption was an exception to the rule that actinide absorption was greatly enhanced in neonates. Adult rats were reported to absorb about 1% of neptunium administered, similar in magnitude to that absorbed by neonatal rats (see Harrison, 1983b). However, recent work indicates that the high absorption of neptunium by adults is an artifact of the high mass doses administered, and that absorption by adults of the lower masses of concern in radiation protection is much lower. For example, adult rats absorbed 2.7, 1.5, 0.06, and 0.05% of the nitrates of ^{237}Np , ^{237}Np , ^{235}Np , and ^{239}Np , respectively, when gavaged at doses of 4.3×10^4 , 2.2×10^4 , 1.3×10^{-2} , and 2.2×10^{-5} $\mu\text{g}/\text{kg}$, respectively (Sullivan, Miller, and Ryan 1983b). This effect of mass administered on absorption in adults is reviewed by Harrison (1983b).

Absorption of neptunium compounds at low masses is much greater in neonates than in adults. One-day-old rats absorbed 3.5% of ^{235}Np nitrate

Table 10. Absorption of neptunium compounds by young mammals.

Isotope and chemical form	Species	Dose		Number of animals	Age (days)	Total % retained or absorbed ^a	% retained in intestine		Reference
		Mass	Activity				Wall	Contents	
237 nitrate	Rat	$2.8 \times 10^3 \mu\text{g}$	$2.0 \mu\text{Ci}$	3	1	0.75	7.5	7.2	Sullivan (1980b)
				4	2	0.60	22	17	
				9	3	0.37	14	14	
				3	4	0.64	7.7	3.6	
				10	9	1.2 ^b	5.5	7.5	
237 nitrate	Rat	$1.7 \times 10^5 \mu\text{g}/\text{kg}$	$120 \mu\text{Ci}/\text{kg}$	6	1	0.43	(6.1) ^c	Sullivan, Miller, and Ryan (1983b)	
235 nitrate		3.5×10^{-2}	50	9	1	3.5	(56) ^c		
239 nitrate		8.0×10^{-4}	190	9	2	1.3 ^d	(73) ^{c,d}		
239 nitrate		4.3×10^{-4}	100	11	9	0.90 ^d	(60) ^{c,d}		
237 nitrate	Rat	$9.5 \times 10^4 \mu\text{g}/\text{kg}$	$68 \mu\text{Ci}/\text{kg}$					Sullivan, Ruemmler, and Ryan (1984)	
Oxidizing or reducing agent administered (dose, mg/kg)									
----(0)				15	5	0.91	(12) ^c		
Fe^{3+} (50)				10	5	1.10			
Fe^{3+} (90)				10	5	1.13	(24) ^c		
Fe^{3+} (180)				9	5	2.7			
Fe^{2+} (190)				8	5	0.12			
237 nitrate	Swine	$\sim 2.5 \times 10^4 \mu\text{g}/\text{kg}$	$15\text{-}20 \mu\text{Ci}/\text{kg}$	4	1	6.1	4.1 ^e	Sullivan and Gorham (1982)	
239 nitrate	Hamster	$4 \times 10^{-5} \mu\text{g}$	$3 \times 10^{-8} \mu\text{Ci}$	6	2	2.5		Harrison and David (1984)	
				6	4	1.7			
239 bicarbonate	Hamster	$5 \times 10^{-5} \mu\text{g}$	$4 \times 10^{-8} \mu\text{Ci}$	10	2	5.5		Harrison and David (1984).	
				10	4	2.1			

^aAmount retained in body, except GI tract, after 7 days except as noted. Results of Harrison and David are by a different method, wherein retention in certain tissues is compared with retention after injection of neptunium and thus is an estimate of absorption.

^bThis experiment is apparently the same as that reported in Sullivan and Crosby (1975,1976), with retention reported as 6.6% and 1.2%, respectively, and age reported as 8 days. Table 2 of Harrison's review (1983b) lists this as two separate experiments.

^cWall and contents combined.

^dAnimals were sacrificed 4 days after gavage.

^eNot clear whether this includes the contents also.

administered at 3.5×10^{-2} $\mu\text{g}/\text{kg}$; two-day-old rats absorbed 1.3% of ^{239}Np nitrate at 8.0×10^{-4} $\mu\text{g}/\text{kg}$; and two-day-old hamsters absorbed 2.5 and 5.5% of ^{239}Np nitrate and bicarbonate, respectively, at about 10^{-2} $\mu\text{g}/\text{kg}$ (Sullivan, Miller, and Ryan 1983b; Harrison and David 1984). Thus neptunium is similar to plutonium, americium, and curium in this regard.

The percentage of neptunium absorbed by neonates appears to decrease with increasing mass administered, contrary to the pattern seen in adults. One-day-old rats absorbed 3.5% of ^{235}Np nitrate administered at 3.5×10^{-2} $\mu\text{g}/\text{kg}$ but only 0.4% of ^{237}Np nitrate administered at 1.7×10^5 $\mu\text{g}/\text{kg}$ (Sullivan, Miller, and Ryan 1983b). The percentage of neptunium retained tenaciously in the intestine may also be sensitive to the mass administered -- in these two groups 56% and 6%, respectively, was retained in the intestinal wall and contents seven days after gavage. Two- and nine-day-old rats also given low mass doses retained 73% and 60% in their intestinal wall and contents four days after gavage. Rats of ages 1-9 days given a high mass dose of ^{237}Np nitrate (2.8×10^3 μg) retained 11-39% in their intestine and contents seven days after gavage (Sullivan 1980b). This retention is similar in magnitude to that seen for plutonium. However, this effect has not been studied systematically.

The effects of oxidizing and reducing agents and fasting on absorption of neptunium in adults are consistent with the hypothesis that at low mass doses in fed adult animals Np(V) is reduced to Np(IV) in the intestine, and this Np(IV) is not absorbed as readily as Np(V) (Sullivan, Ruemmler, and Ryan 1984). At high mass doses the capacity of the intestine to reduce Np(V) is then overwhelmed. In the neonate less is known about the effect of intestinal contents on absorption, and the experimental results of oxidizing and reducing agents on absorption in neonates are also less clear. Absorption of ^{237}Np nitrate by five-day-old rats at a high mass dose (9.5×10^4 $\mu\text{g}/\text{kg}$) decreased from 0.91 to 0.12% when a reducing agent (ferrous ion) was added. When an oxidizing agent (ferric ion) was added at a mass of 18×10^4 $\mu\text{g}/\text{kg}$, absorption, estimated as retention in lung, liver, and carcass, was said to increase from 0.91 to 2.7%. However, reported retentions in lung, liver, and femur were approximately the same in the two groups (0.002 vs 0.002%, 0.024 vs 0.03%, and 0.016 vs 0.02%, respectively).

The effect of chemical form on absorption has been little studied. Two-day-old hamsters absorbed $2.5 \pm 0.3\%$ (mean \pm S.E.M.) of ^{239}Np nitrate and $5.5 \pm 1.7\%$ of ^{239}Np bicarbonate, suggesting that bicarbonate may be more readily absorbed (Harrison and David 1984). However, the difference is not significant at the 5% level when tested with a t-test modified to take into account the highly significant difference in the variances of the two samples (Sokal and Rohlf 1969, p. 374).

The effect of age during the suckling period has also been little studied. In hamsters absorption of ^{239}Np nitrate decreased from $2.5 \pm 0.3\%$ at age 2 days to $1.7 \pm 0.3\%$ at age 4 days; absorption of ^{239}Np bicarbonate decreased from $5.5 \pm 1.7\%$ at age 2 days to $2.1 \pm 0.4\%$ at age 4 days (Harrison and David 1984). These results suggest a decreasing absorption with age, similar to that seen with plutonium; however, neither of these differences was significant statistically. In rats absorption of ^{237}Np nitrate was measured at ages 1, 2, 3, 4, and 9 days (Sullivan 1980b), but no pattern is apparent and a high mass was administered (see Table 10).

There is no information on the site or mechanism of absorption for neptunium in neonates.

For the purpose of radiation protection from environmental contamination by neptunium, Harrison (1983b) recommends that a value of 1% absorption be applied to infants 0-3 months of age who are fed exclusively with a milk diet, a value of 0.1% be applied after 9 months of age, and an averaged value of 0.5% be applied to infants 0-12 months old. These values are for all chemical forms of neptunium. Harrison's value for children older than nine months and adults is one-tenth that currently recommended by the ICRP (1980) for radiation workers. Harrison (1983b), Thompson (1982), and Sullivan, Ruemmler, and Ryan (1984) have recommended that the value for workers be reduced.

Our recommendations (Table 12) are similar, except that we recommend 0.2% absorption by children older than nine months.

Other Actinides

The scant data available on absorption of other actinides by neonates is given in Table 11. There is no information on site or mechanism of absorption for any of these actinides.

Table 11. Absorption of other actinides by young mammals.

Element and chemical form	Species	Dose		Number of animals	Age (days)	Total % retained ^a	% retained in intestine		Reference
		Mass	Activity				Wall	Contents	
Th-228 nitrate	Rat	8 μ g	0.1 μ Ci	11	2	1.2	6.8	5.0	Sullivan (1980b)
Th-228 nitrate	Rat	8000 μ g/kg	100 μ Ci/kg	18	2	1.1	(18) ^b		Sullivan, Miller, and Ryan (1983a)
Pa-233 nitrate	Rat	0.0001 μ g/kg	18 μ Ci/kg	28	2	2.6	(60) ^b		Sullivan, Miller, and Ryan (1983a)
U-232 (uranyl) nitrate	Rat	0.12 μ g	2.5 μ Ci	5	2	6.7	4.5	2.5	Sullivan (1980b)
		210	2.0	5	2	1.3	0.97	0.32	
U-233 (uranyl) nitrate	Swine	2400 μ g/kg	23 μ Ci/kg	3	1	35	4.1	8.7	Sullivan and Gorham (1982); Sullivan (1979)
				3	1	38	1.7	0.07	
				3	1	37	1.2	0.03	
U-233 oxide (U ₃ O ₈), polydispersed	Rat	220 μ g	2.1 μ Ci	11	2	0.36	0.25	0.070	Sullivan (1980b)
Cf-252 nitrate	Rat	0.0045 μ g	2.5 μ Ci	7	2	2.5 ^c			Sullivan (1980b)
Es-253 nitrate	Rat	0.0002 μ g	5.0 μ Ci	8	1	4.3 ^d	0.77	6.8	Sullivan (1980b)

^aAmount retained in body, except GI tract, after 7 days except in the swine, which were sacrificed 12, 21, and 25 days, respectively, after gavage. Retention excludes skin also for swine and for rats of Sullivan, Miller, and Ryan.

^bWall and contents combined.

^cAmount retained in skeleton and liver.

^dSevere damage to intestinal epithelium.

Thorium

Two-day-old rats absorbed 1.1-1.2% of ^{228}Th nitrate given in doses of 800-8000 $\mu\text{g}/\text{kg}$; 12-18% was retained in the intestinal wall and contents seven days after administration (Sullivan 1980b; Sullivan, Miller, and Ryan 1983a). Adult rats absorbed 0.005% of ^{228}Th nitrate given in a dose of 1000 $\mu\text{g}/\text{kg}$, and adult mice absorbed 0.06% of ^{228}Th nitrate given in a dose of 8000 $\mu\text{g}/\text{kg}$ (Sullivan 1980a; Sullivan, Miller, and Ryan 1983a). Adult rats absorbed 0.6% of ^{232}Th nitrate given in a higher dose of 2×10^5 $\mu\text{g}/\text{kg}$ (Traikovitch 1970). These data suggest that absorption of thorium nitrate may be about 100 times higher in neonatal rats than in adult rats, similar to the results with plutonium.

The ICRP (1979) uses a value of 0.02% absorption for all compounds of thorium. This value is based primarily on a study in adult humans in which absorption of ^{234}Th sulfate was in the range of 0.01-0.06%, with an average value of about 0.02%. We suggest that Harrison's recommended values for absorption of soluble compounds of plutonium and all chemical forms of americium, curium, and neptunium in the first year of life also be applied to all chemical forms of thorium (see Table 12).

Protactinium

Only one experiment on absorption of protactinium by neonates has been reported. Two-day-old rats absorbed 2.6% of ^{233}Pa nitrate given in a dose of 10^{-4} $\mu\text{g}/\text{kg}$; 60% was retained in the intestinal wall and contents seven days after gavage (Sullivan, Miller, and Ryan 1983a). These workers also reported that adult rats absorbed 0.03% of ^{233}Pa given in a dose of 6×10^{-5} $\mu\text{g}/\text{kg}$, suggesting that protactinium is similar to the other actinides in a greatly increased absorption by neonates.

Other experiments with adult rats and hamsters, with different chemical forms and at different masses administered, indicate that it is too soon to make any strong conclusions about the differences in absorption between neonates and adults. Hamilton (1948) reported that absorption by rats of ^{231}Pa in isotonic saline was less than 0.05%; the amount administered was not given. Zalikin reported that retention by

rats of ^{233}Pa in citric acid solution "does not exceed 1-2%" when administered at $1.4 \times 10^5 \mu\text{g}/\text{kg}$ (Zalikin 1966a, p. 42). He also reported that 0.02-0.03% was retained when ^{233}Pa citrate was given in a 0.2% solution and 0.2% was retained when given in a 2% solution (Zalikin 1966b; total amount administered was not specified). Daily administration of $7 \times 10^5 \mu\text{g}/\text{kg}$ of ^{233}Pa in citric acid solution resulted in retention of about 0.1% after 8 days (Zalikin 1969). Harrison and Stather (1981) reported that hamsters absorbed 3.9% of ^{233}Pa citrate and 0.22% of ^{233}Pa fluoride when administered at approximately $300 \mu\text{g}/\text{kg}$, and they suggest that the lower absorption of the fluoride was probably a result of hydrolysis in the intestine.

On the basis of the work by Hamilton and by Zalikin, the ICRP (1981) has recommended that absorption by workers be taken as 0.1% for all chemical forms of protactinium. Harrison and Stather (1981) suggest, on the basis of their work with hamsters, that the ICRP value may be too low and that a value of 1% may be more appropriate. Since little systematic work on the effects of chemical form, mass administered, species, and age has been done to explain these differences in absorption, it would be prudent to use a value of 1% for all ages (see Table 12).

Uranium

For absorption by workers, the ICRP (1979) has recommended a value of 5% for the water-soluble hexavalent inorganic compounds of uranium, such as uranyl nitrate and uranyl fluoride, and a value of 0.2% for the relatively insoluble (usually tetravalent) compounds such as UF_4 , UO_2 , and U_3O_8 . On the basis of their results for absorption of ^{233}U (uranyl) nitrate in adult hamsters and their review of the literature, Harrison and Stather (1981) recommend a value of 1% for the soluble hexavalent forms. Wrenn et al. (1985) have reviewed the literature -- for both adults and neonates -- relevant to deriving drinking water standards. They recommend a value of 1-2% for the soluble hexavalent forms, and they state that it is "probably reasonably independent of age or the mass of U ingested" (p. 601). We do not believe that present information is strong enough to support this statement, however.

Moreover, it appears that the absorption fraction for uranium may depend on the level of intake, particularly near typical environmental levels. The value recommended by Wrenn et al. may be reasonable for adults at intake levels several times the normal background level. Our own preliminary analysis of uranium in autopsy samples (liver, kidneys) of persons apparently exposed only to normal background levels indicate an absorption fraction in the range 10-30%.

The scant data on absorption of uranium compounds by neonates is given in Table 11. When two-day-old rats were gavaged with ^{232}U (uranyl) nitrate at a dose of about $12 \mu\text{g}/\text{kg}$, 6.7% was retained in the body (excluding the intestinal wall and contents) seven days after administration. When the dose was about $2.1 \times 10^4 \mu\text{g}/\text{kg}$, 1.3% was so retained (Sullivan 1980b; a body weight of 10 g was assumed in deriving mass-per-kg administered). In contrast, adult rats retained 0.01-0.02% of uranyl nitrate in the skeleton and liver seven days after administration of doses of 2×10^6 to $3 \times 10^4 \mu\text{g}/\text{kg}$; adding excretion in urine over the seven days led to an estimate of absorption of 0.04-0.09% (Sullivan 1980a; Sullivan, Miller, and Ryan 1984; and see Wrenn et al. 1985). These data suggest that as much as 25-30% of uranyl nitrate could be absorbed by the neonate at the lower dose administered, if retention and excretion in urine are similarly related in the neonate. However, excretion in urine by the neonate has not been measured, and it is plausible that retention of uranium in the growing skeleton of the neonate could be higher than in the adult, relative to excretion.

Two-day-old rats retained 0.36% of ^{233}U oxide (U_3O_8) seven days after gavage with a dose of about $2.2 \times 10^4 \mu\text{g}/\text{kg}$ (Sullivan 1980b). Adult rats retained 0.006% of ^{233}U oxide in the skeleton and liver seven days after gavage with a dose of about $2.6 \mu\text{g}/\text{kg}$; adding excretion in urine over the seven days led to an estimate of absorption of 0.037% (Sullivan 1980a). These results suggest that absorption of the oxide may be substantially higher in neonatal rats, but the difference in doses administered precludes any strong conclusion.

In their review Wrenn et al. (1985) present data that suggest that absorption of soluble compounds of uranium by the rat is substantially different from that by other mammals (hamster, rabbit, dog, baboon, and

man). A regression line with the rat data suggests that absorption falls from 0.15 to 0.05% as the uranium intake rises from 10^{-2} to 10^6 $\mu\text{g}/\text{kg}$ in a single dose or in daily doses. A regression line with data from all other species suggests that absorption falls from 3 to 0.3% over the same range in intake. Wrenn et al. conclude that the rat is not a good model species for absorption of soluble uranium compounds. The significance of the enhanced absorption by neonatal rats to human infants is thus even more problematical for uranium than it is for other actinides.

One-day-old swine retained 35-38% of ^{233}U (uranyl) nitrate in their bodies 12-25 days after gavage with a dose of 2400 $\mu\text{g}/\text{kg}$ (Sullivan 1979; Sullivan and Gorham 1982). This result is similar to that with plutonium nitrate in neonatal swine (Table 4), and this bulk absorption may be related to the bulk absorption of macromolecules in the immediate postnatal period in this species. Thus this finding probably has no significance for absorption by humans.

Californium and Einsteinium

For workers the ICRP (1979, 1981) recommends an absorption value of 0.05% for all compounds of californium and einsteinium. This recommendation is based on the available data in adult mammals, which suggest that absorption of these two elements is similar to that of americium.

The scant data (one experiment for each element -- see Table 11) suggest that the nitrates of californium and einsteinium are absorbed more readily by neonatal rats than by adult rats, and the magnitude of the increased absorption is similar to that for the nitrates of plutonium, americium, and curium. We suggest that Harrison's recommended values for absorption of soluble compounds of plutonium and all chemical forms of americium, curium, and neptunium in the first year of life also be applied to all chemical forms of californium and einsteinium (see Table 12). These values are tentative, because possible confounding effects of chemical form, mass administered, age, and species have not been studied. They are especially tentative for einsteinium, in which there was severe damage to the intestinal epithelium in the neonatal rats studied.

Our recommended values for absorption of californium and einsteinium compounds by adults and by children older than nine months (Table 12) are the same as for soluble forms of plutonium and all forms of americium, curium, and neptunium.

Table 12. Recommended values for absorption of actinides from the intestine.

Element	Chemical form	Absorption (%)				
		Worker ^a	Public ^b			
			Adults	Children ^c	Infants 0-12 mo ^d	Infants 0-3 mo ^e
Pu	oxides, hydroxide	0.001	0.001 ^f	0.002	0.05 ^f	0.1 ^f
	All other forms	0.01	0.1 ^{g,h}	0.2	0.5 ^f	1 ^f
Am, Cm	All forms	0.05	0.1 ^g	0.2	0.5 ^f	1 ^f
Np	All forms	0.1	0.1 ^f	0.2	0.5 ^f	1 ^f
Th	All forms	0.02	0.02	0.05	0.5	1
Pa	All forms	1	1	1	1	1
Cf, Es	All forms	0.05	0.1	0.2	0.5	1
U	hexavalent	5 ⁱ	? ⁱ	? ⁱ	? ⁱ	? ⁱ
	All other forms	0.2 ⁱ	? ⁱ	? ⁱ	? ⁱ	? ⁱ

^aICRP (1979,1980,1981) values for inorganic forms, except for Np, which is that recommended by the NRPB (1984), and Pa, which is that recommended by Harrison and Stather (1981).

^bValues for radionuclides in food and water.

^cChildren older than nine months.

^dAverage absorption for the first year of life (after NRPB, 1984).

^eAverage absorption when infants are assumed to be fed exclusively with a milk diet (after NRPB, 1984).

^fSame as that recommended by the NRPB (1984).

^gTwo times that recommended by the NRPB (1984).

^hThe NRPB (1984) recommends that 0.01% absorption be used when inorganic forms of Pu are adsorbed to food, and 0.05% be used when Pu is biologically incorporated in the food or the relative amounts of adsorbed and incorporated Pu are not known.

ⁱThe experimental evidence for uranium is not clear. See text. The recommended value for a worker assumes an intake that is several times the normal intake for nonoccupational exposures.

Strontium

Suckling rats absorb nearly all the strontium given by gavage. In an experiment with rats weaned at age 28 days, Taylor et al. (1962) reported that rats 14-18 days old absorbed 95% of ^{85}Sr chloride, rats 22 days old absorbed 74%, rats 6-8 weeks old absorbed 25%, and adults 60-70 weeks old absorbed 11%. Note that the weaned juvenile rats absorbed twice as much strontium as did the adults, and this difference was highly significant ($24.6 \pm 1.0\%$ vs $11.1 \pm 0.8\%$; these are means \pm S.E.M., and $n=45$ and $n=24$, respectively). They reported similar results with the chemically similar element calcium, except that the weaned juveniles and the adults absorbed a greater percentage of calcium than strontium -- absorption by rats of ages 14-18 days, 6-8 weeks, and 60-70 weeks was 98, 63, and 32%, respectively. (Strontium follows calcium pathways closely, and it is often used as a marker for calcium in intestinal absorption studies -- Gmaj and Murer, 1984.)

In an experiment with rats weaned at age 22 days, Forbes and Reina (1972) reported that absorption of ^{85}Sr (chloride?) declined from 85% at age 15 days to 79, 73, 54, 36, 15, and 8% at ages 17, 20, 22, 24, 39, and "89+" days, respectively. The difference in absorption between the last two groups -- the 39-day-old weaned juveniles and the "89+"-day-old rats -- is similar to the two-fold difference between the 6-to-8-week-old and 60-to-70-week-old rats above, but the difference is not significant statistically at the 5% level ($15.3 \pm 4.8\%$ vs $8.2 \pm 3.6\%$; these are means \pm S.E.M., and $n=6$ and $n=5$, respectively).

Metabolic balance studies with ^{90}Sr and stable strontium in normal diets by human infants of ages one month to one year have been reported by Kahn et al. (1969). Apparent absorption, measured as intake minus fecal loss, was 25%, which is within the range of 10-35% reported by others for adults; and true absorption was 41%, which is similar to the "approximately 40%" absorption reported by others for adults (see Kahn et al. for references). They concluded that the percentage absorption of both strontium and calcium is similar in human infants and adults.

Harrison (1959) reached a different conclusion on calcium absorption by infants, based on several studies with subjects said to "have been ingesting high calcium intakes, with a calcium to phosphorus

ratio in the range of normal diets [and with] adequate amounts of vitamin D" (p. 1089). Apparent absorption (intake - fecal excretion) was about 70% in premature infants, about 50% in infants less than six months old, and about 40% in infants ten months old. However, apparent absorption was less than 20% in children 3-5 years old and in adults.

In cattle and rats true absorption of calcium, as calculated from simultaneous chemical and radioisotope balance studies and corrected for fecal excretion of endogenous calcium, is much higher in neonates than in older animals (Hansard et al. 1954; Hansard and Crowder 1957). Absorption by 10- and 30-day-old unweaned calves was 98%; in 6-month-old weaned calves absorption was 41%; in 1- and 2-year-old and in "mature" cattle absorption was about 35%; and in "aged" cattle absorption was 22%. Absorption by 4-week-old weanling rats was 98%, which declined to 57, 46, 41, and 24% in rats of ages 12, 24, 48-72, and 106 weeks, respectively.

We conclude that absorption of strontium by infants is probably between one and two times that by adults, and the amount of dietary calcium may affect the percentage absorbed. Absorption by neonates may approach 100%.

Iron

Enhanced absorption of iron by the young is of interest because of the similar chemical and physiological properties of Fe(III) and Pu(IV) and the possibility that factors that influence absorption of iron may also influence absorption of plutonium. "Some of the most stable complexes known are formed by Fe(III), and in the chemical properties that largely determine complex stability -- high positive charge, small ionic size, and high acidity -- Pu(IV) and Fe(III) are similar. Their charge: radius ratios are 444 and 460 e/ μm , respectively [Shannon 1976]. Thus ligands with donor groups favoring formation of stable Fe(III) complexes are likely to be effective for Pu(IV)" (Durbin et al. 1980, p. 172). Plutonium follows iron pathways in the body, at least in part. Pu(IV) combines with the iron-transport protein, transferrin, in the blood of rats, dogs, and humans (Boocock and Popplewell 1965; Popplewell and Boocock 1967; Turner and Taylor 1968; Stover, Bruenger, and Stevens 1968; Stevens, Bruenger, and Stover 1968). Plutonium is associated with

the iron-storage proteins ferritin in hepatic cells and hemosiderin in reticuloendothelial cells in dogs (Taylor et al. 1966, 1967; Bruenger, Stover, and Stevens 1971). Plutonium and iron appear to share common pathways of metabolism in macrophages in rats (Priest and Haines 1982). Iron-deficient mice, which are known to absorb more iron than iron-replete mice, also absorb 4-5 times more plutonium citrate than do iron-replete mice (Ragan 1974). Whether plutonium is absorbed in whole or in part by the same mechanism as non-heme iron is not known, however.

Several studies on the absorption of ^{59}Fe by human infants and children have been reported. Absorption was measured as the difference between the amount of radioiron ingested and that found in the feces. Garby and Sjolín (1959) gave a solution containing ^{56}Fe citrate and tracer ^{59}Fe with a milk meal to nine infants of age 10-90 days (Figure 4). There appears to be a rapid decrease in absorption with increasing age; the four infants younger than 1.5 months absorbed 56-91% of the ^{59}Fe , and the five infants 1.5-3 months old absorbed 15-38%. In another study 15 infants and children 4-52 months old were given either ^{59}Fe sulfate added to cow's milk (milk labelled "in vitro") or milk from cows which had been given ^{59}Fe (milk labelled "in vivo") (Schulz and Smith 1958). The amount of ^{59}Fe absorbed by these subjects is also shown in Figure 4. Absorption was $10.6 \pm 2.7\%$ (mean \pm S.E.M.) and $9.1 \pm 1.1\%$ for the milk labelled in vitro and in vivo, respectively. The milk labelled in vivo was also fed to six adult males, who absorbed $2.8 \pm 0.9\%$, or about one-third of what the young children absorbed.

Absorption of ^{59}Fe by 14 healthy premature infants of age 1-10 weeks has been reported by Gorten et al. (1963). ^{59}Fe chloride was reduced with ascorbic acid and added to a prepared milk formula (ascorbic acid enhances absorption of iron [Underwood 1977, p. 25]). Absorption varied from 6.8 to 74% with a mean of 32%. There was some correlation between absorption and chronological age, but it was not statistically significant. No correlation between absorption and gestational age, birth weight, or weight of infant at time of administration of the iron was observed. However, there was a strong and highly significant correlation between absorption and rate of weight gain (in g/kg body weight/day), with the faster growing infants absorbing a greater

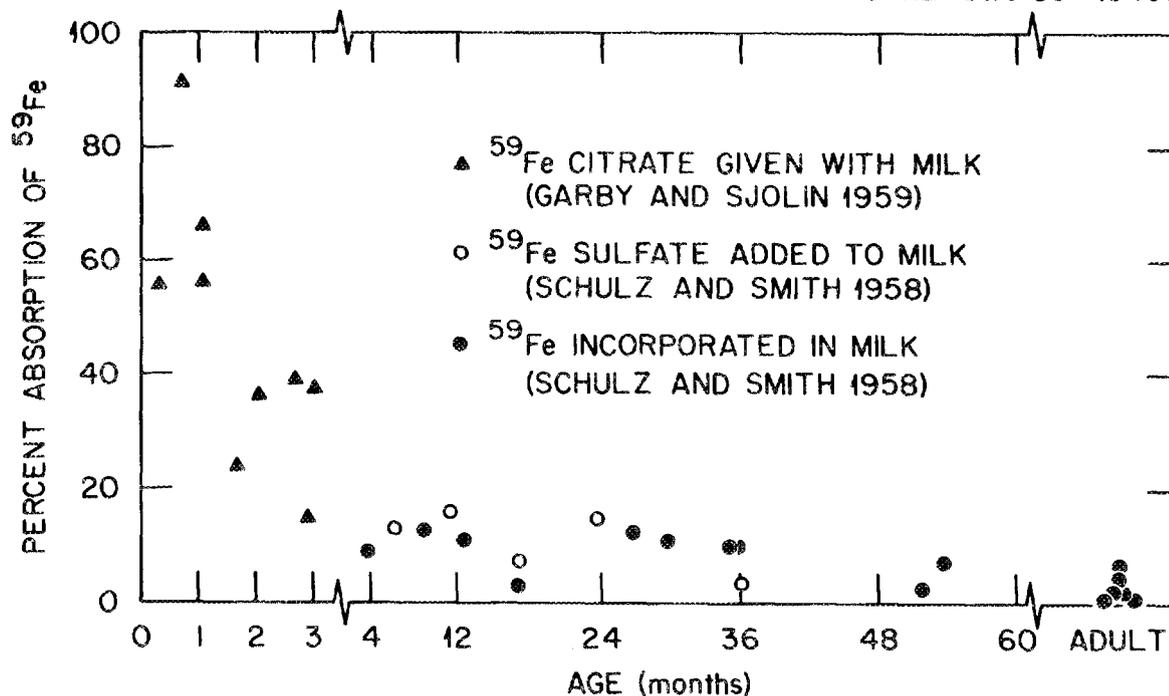


Figure 4. The absorption of ^{59}Fe administered with milk as a function of age. (Adapted from Garby and Sjolín, 1959).

percentage of iron; and in their Fig. 1 the logarithm of percentage absorption and the rate of weight gain appear to be linearly related.

These values for premature infants are somewhat lower than those reported for the normal-term infants of Garby and Sjolín (above) when compared on the basis of chronological age, but they are similar when compared on a graph of $\log(\% \text{ absorption})$ vs rate of weight gain (see Fig. 4 of Gorten et al.; note, however, that the rate of weight gain used for the premature infants was measured, but the rate for the other infants studied by Garby and Sjolín was assumed to be the average value for the chronological age reported; note also that the weight gain in their Fig. 4 is given in g/day instead of g/kg/day, with the relationship still appearing linear.)

Also plotted in Fig. 4 of Gorten et al. are data of Schulz and Smith (1958) on absorption of ^{59}Fe in milk, cereal, or egg by infants and

children 4 months to 15 years old. Both absorption and (assumed) rate of weight gain are lower than for the neonates, but we are not convinced that a correlation between the two variables can be shown for this period of age using these data.

In an attempt to determine the differences in iron absorption in children of different ages, Schulz and Smith (1958) fed eggs labelled in vivo with ^{59}Fe to 52 children of ages 1-15 years. The 29 children of ages 1-4.5 years absorbed $11.0 \pm 1.4\%$ (mean \pm S.E.M.) and the 23 children of ages 5-15 years absorbed $5.5 \pm 0.9\%$. They compared their results with those of Moore and Dubach (1951), who fed similarly labelled eggs to healthy young adults. The six males in this study absorbed $2.7 \pm 0.9\%$ and the three females absorbed $6.9 \pm 1.3\%$, with the difference between the males and females significant at $p < 0.05$. However, direct comparison between these results and those for children is problematical, because absorption in the adults was estimated by incorporation of ^{59}Fe into circulating hemoglobin, and absorption in the children was estimated as the amount of ^{59}Fe not appearing in feces.

Absorption of ^{59}Fe by children 7-10 years of age was studied by Darby et al. (1947). An aliquot of 2-3 mg of ferrous chloride containing ^{59}Fe , reduced with a slight excess of ascorbic acid, was fed in lemonade to 176 children at least an hour before or after lunch (both ascorbic acid and citric acid enhance iron absorption [Underwood 1977, p. 25]). The results are shown in Table 13. The eight-year-old girls and the nine- and ten-year-old boys and girls absorbed substantially more ^{59}Fe than did the seven-year-old boys and girls and the eight-year-old boys. There was no correlation between absorption and hemoglobin concentration in the blood measured in these subjects, but there was a correlation between absorption and total yearly iron requirement for boys and girls estimated by others. If the yearly iron requirement is normalized per kg body weight, the correlation still holds. Absorption by adults with this protocol was not measured.

Conclusions

Iron absorption in infants falls rapidly from a high of 50-100% in the first month of life to about 10% by four months of age. Premature

Table 13. Absorption of ^{59}Fe by children 7-10 years old.^a

Age	7 years		8 years		9 years		10 years	
	male	female	male	female	male	female	male	female
Number	17	24	26	34	26	23	17	9
Mean	9.3	7.8	10.4	15.8	16.1	16.9	16.7	14.5
± S.E.M. (%)	±1.4	±0.8	±1.2	±2.2	±1.0	±2.0	±1.9	±2.4
Median (%)	7.8	7.0	8.3	12.0	15.0	13.8	17.8	12.8
Estimated total yearly iron requirement (mg) ^b	70	67	72	108	152	120	130	163

^aFrom Darby et al. (1947); note that the iron was reduced by a slight excess of ascorbic acid and fed in lemonade -- both ascorbic acid and citric acid enhance iron absorption.

^bData of Heath and Patek (1937), as quoted by Darby et al. (1947).

infants of a given chronological age that are growing more slowly than normal infants of the same age appear to absorb less iron, but absorption is similar if the absorption is compared on the basis of growth rate. From the data of Schulz and Smith (1958), it appears that absorption remains at about 10% from four months to 4-5 years of age but falls to about 5% in children 5-15 years of age. From the data of Darby et al. (1947), it appears that children 9-10 years old absorb more iron than do children 7 years old, and the difference may be related to growth requirements for iron. It is not known whether absorption is increased still further during the adolescent growth spurt. The percentage absorbed by children will be higher than these values if substantial amounts of reducing agents are consumed with the iron. It appears that children past infancy probably absorb more iron than do adults. However, in only one experiment with ^{59}Fe did the authors study both children and adults with the same protocol.

Because of the similarities between iron and plutonium and because absorption of plutonium and other actinides in children is not known, it may be prudent to assume that actinide absorption is about three times the adult level in children from weaning to five years of age and about two times the adult level from five years to adulthood.

Lead

Absorption of lead by the young is of interest for the following reasons: (1) Human infants and children well past weaning absorb much more lead than do adults. Absorption of lead by young rats decreases rapidly at or shortly after weaning to much lower levels, similar to the pattern for other metals including actinides. However, it is not clear whether absorption of lead by weaned juvenile rats is at adult levels, as has been reported, or whether absorption may be as much as 2-3 times higher than in adults. The rat may not be a good model for lead absorption in humans between weaning and adulthood. Whether the weaned juvenile rat is a good model for absorption of other metals during late infancy and childhood and whether it is safe to assume that absorption of actinides by humans reaches adult levels soon after weaning need to be investigated more critically. (The high absorption of lead in children may be related only to the high demand for calcium [Task Group 1973], and the mechanism for high calcium absorption may have no effect on actinide absorption; but it illustrates the weakness of the rat model for children.) (2) The mechanisms and sites of absorption of lead during the neonatal period are better characterized than for other metals. It is not clear how much of these results will apply to other metals, but the experimental methods might be used to study the mechanism(s) and site(s) of absorption of actinides, where the experimental evidence is less clear-cut.

Absorption by Infants and Children

Ziegler et al. (1978) performed 89 metabolic balance studies with 12 normal infants and children ranging in age from 2 weeks to 2 years. The amount of stable lead in the food fed to these children was measured (no lead was added to food), and the amounts of lead in feces and urine were also measured. Net (or apparent) absorption was defined as the intake minus the fecal excretion of lead, and net retention was defined as the net absorption minus the urinary excretion of lead. In some subjects with low intakes of lead, net absorption and net retention were negative; and net absorption and net retention of lead, expressed as percentage of intake, increased significantly with increasing lead

intake. These results were interpreted as resulting from relatively high fecal excretion of endogenous lead. Thus at higher intakes of lead, net absorption should approach true absorption. In those subjects with intakes of lead greater than 5 $\mu\text{g}/\text{kg}/\text{day}$, net absorption averaged 42% of intake and net retention averaged 32% of intake, and there were no significant differences with age. Alexander et al. (1974) reported similar results from eleven balance studies with eight children ranging in age from three months to eight years: with intakes ranging from 5-17 $\mu\text{g}/\text{kg}/\text{day}$, net absorption averaged 53% of intake and net retention averaged 18% of intake. Average net absorption in adults, reported by others, is much lower, ranging from 4 to 10% (see Ziegler et al., 1978, and Willes et al., 1977, for references).

Absorption by Juveniles of Other Species

In contrast Forbes and Reina (1972) reported that absorption of lead by juvenile rats may reach adult levels shortly after weaning. Average absorption of ^{212}Pb (the nitrate mixed with saline) was 83-90% when it was administered at 16, 18, or 20 days of age, fell to 74% at 22 days (age of weaning), and fell further to 42%, 37%, and 15% at 24, 27, and 32 days of age, respectively. The latter value is similar to the percentage absorbed by rats of age "89+" days in their experiment (16%). However, the experiment was not designed to test for differences of, say, 2-to-3-fold between weaned juveniles and adults. The numbers of animals are small and the 95% confidence limits are large in the latter two groups: at age 32 days absorption was 15% with 95% C.L. of 2-28% ($n=6$) and at age 89+ days absorption was 16% with 95% C.L. of 10-22% ($n=3$). In addition, the animals of age 89+ days may still have been growing and may not have reached adult values of absorption, even though they may have been sexually mature (for example, compare the results of Taylor et al. (1962), where absorption of calcium, strontium, and radium was 2-3 times higher in rats 6-8 weeks old than in rats 60-70 weeks old). Whether weaned juvenile rats are an adequate model for absorption of lead by children after infancy is not clear from these results.

Willes et al. (1977) have demonstrated that infant and juvenile monkeys (species Macaca fascicularis) may be a good model for lead absorption by human infants and children. They administered ^{210}Pb

nitrate (10 µg/kg by gavage) to monkeys of ages 10 days and 150 days and to adults; there were four animals in each age group, and the animals had fasted 12 hours before administration. The 10-day-old infants received a diet of infant formula; the 150-day-old infants received infant formula, a commercial primate diet, and fresh fruits (i.e., they were partially weaned); and the adults received the primate diet and fresh fruits. (There were no substantial differences among the three groups in calcium, vitamin D, or phosphate intake. For a discussion of other dietary factors that can affect lead absorption, see Willes et al.) Urine and feces were collected for 96 hours after dosing, and the monkeys were sacrificed at 96 hours for analysis of tissues. The 10- and 150-day-old infants retained $65 \pm 2.5\%$ (mean \pm S.E.M.) and $70 \pm 2.5\%$, respectively, of the lead administered, and the adults retained $3.2 \pm 3.3\%$ (absorption was only slightly higher, as urinary excretions were measured as 2.2, 1.6, and 0.8%, respectively, of the administered dose). The results from one monkey discarded from the statistical comparisons suggest that absorption of lead may remain high throughout the juvenile period: this monkey had been classed as an adult at the start of the experiment, but it showed a nonadult distribution pattern of lead in bone and it had immature ovaries and open epiphyseal junctions in the humerus and femur. This late-juvenile monkey, fed the adult diet, retained 56% of the ^{210}Pb administered.

Small or no difference between adult and infant monkeys in absorption of lead has been reported by Pounds et al. (1978), however. They administered ^{210}Pb acetate (10 mg/kg by gavage) to four infant (5-7 months of age) and four adult (7-10 years of age) rhesus monkeys (Macaca mulatta). All monkeys were fed a commercial chow and water. The infants absorbed $38 \pm 3.5\%$ (mean \pm S.E.M.) and the adults absorbed $26 \pm 4.7\%$; the difference is at the borderline of significance ($p < 0.1$). It is not clear why the results of this experiment are so different from the results of Willes et al. -- species, age, diet, use of fasted animals, and amount and chemical form of lead administered all varied between experiments.

It may be necessary to use a primate model to answer with more confidence the question of when actinide absorption falls to adult levels in humans. However, even with primates there may be serious

experimental difficulties in obtaining a clear-cut answer, as the differences between the results of Willes et al. (1977) and Pounds et al. (1978) with lead demonstrate.

Mechanisms and Sites of Absorption in Neonates

The best information available on the mechanisms and sites of absorption of lead by neonates comes from a study in the mouse by Keller and Doherty (1980a) and a study in the rat by Henning and Leeper (1984). There appear to be important differences in the mechanisms and sites of absorption in these two rodent species. Pinocytosis appears to be an important part of absorption by the suckling mouse, but there is also another absorptive path independent of pinocytosis. In the suckling rat, there is a correlation between pinocytosis and retention within the epithelial cells of the ileum, but the lead so retained appears not to be transferred to the circulation but instead is probably returned to the lumen when the epithelial cell is shed; absorption occurs in the duodenum by a different mechanism independent of pinocytosis. In the mouse, the absorption of lead that is not associated with pinocytosis occurs in the jejunum. The nature of the non-pinocytotic uptake (e.g., a carrier-mediated process associated with calcium or iron uptake, or simple diffusion) is unknown.

Keller and Doherty (1980a) administered lead acetate (5 mg/kg) with tracer amounts of ^{210}Pb and radioiodine-labelled polyvinylpyrrolidone (PVP) by stomach intubation to 12-day-old suckling mice and to adult mice. (PVP is a macromolecule shown to be a marker for pinocytosis in rats (Clarke and Hardy 1969, 1971); it is taken up by pinocytosis into the epithelial cells of the distal small intestine but not transferred to blood.) The mice were killed at various intervals from 0.5 h to 3 days after administration and the small intestine was divided into 24 segments of equal length for analysis of lead and PVP content in the intestinal tissue. The distal jejunum and ileum contained the greatest quantities of both lead and PVP, and the duodenum contained almost no lead or PVP. Lead content was greatest at 0.5 h after administration (the first time studied), was less at 3 h and was very much less at 5.5 h and at 1 and 2 days; this pattern is consistent with lead being

transferred to the circulation. Pretreatment of suckling mice with cortisone, which induces premature closure of the intestine in rats and mice, resulted in decreased content of lead and PVP within tissue of the intestine and also decreased whole-body lead retention. In adult mice lead and PVP uptake into the intestinal tissue was much less than in suckling mice and there were no regional differences in uptake; cortisone administration had no effect on uptake of lead or PVP or on whole-body retention of lead. This evidence strongly suggests that in the neonatal mouse lead is being taken up into the epithelial cells by pinocytosis and is then transferred into the circulation. However, the results of another experiment suggest that lead is also absorbed by another mechanism in neonatal mice. Lead was injected directly into the lumen of either the proximal jejunum, where pinocytosis does not occur, or into the ileum of 12-day-old mice which either had been treated with cortisone or were untreated controls. Mice were killed one hour later, and it was determined that the injected solution remained at or near the site of injection during the one-hour period. Absorption of lead into the body from the ileum was substantially lower for cortisone-treated mice than for controls, but there was no difference between treated and control mice for absorption from the jejunum.

Henning and Leeper (1984) administered ^{203}Pb chloride (carrier-free) plus nonlabelled lead acetate (50 mg/kg) by stomach intubation to suckling rats 10-16 days old and to weanling rats 24 days old. The rats were killed at various intervals from 2 to 24 h after administration and the small intestine was divided in 12 segments for analysis of lead content in the intestinal tissue. At 2 h after administration, the lead content in the proximal intestine, especially in the duodenum, was high in suckling rats but much lower in weanling rats. Lead content in the ileum was low in all groups, but especially in the weanlings. In a second experiment, fasted suckling rats which were not allowed to suckle after administration of the lead took up much more lead than did control rats allowed to suckle afterwards; this suggests that the presence of milk in the intestine was not the reason for the difference between uptakes in the suckling and weanling rats above. The concentration of lead in the blood was much higher in the fasted than in the suckled

rats, suggesting a relation between intestinal uptake and transepithelial transport.

In a third experiment, suckling rats were killed at 2, 4, 6, and 24 h after administration of lead. Lead content in the duodenum was high at 2 and 4 h, lower at 6 h, and virtually undetectable at 24 h. In contrast, lead content in the ileum was lowest at 2 h, intermediate at 4 and 6 h, and highest at 24 h, even though the lead content in the ileal lumen was greatest at 2 h and gradually declined thereafter; this suggests that the lead in the ileal epithelium is not being transported into the circulation.

The differences in these experimental results on mice and rats illustrate the importance of distinguishing between uptake of a metal into the intestinal epithelium and transport of the metal from the epithelium into the circulation. They also illustrate the importance of studying a variety of animal species before attempting to extrapolate to man.

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2. TITLE AND SUBTITLE DETERMINATION OF METABOLIC DATA APPROPRIATE FOR HLW DOSIMETRY. II. GASTROINTESTINAL ABSORPTION		4. DATE REPORT COMPLETED <table border="1" style="width: 100%; text-align: center;"> <tr> <td>MONTH</td> <td>YEAR</td> </tr> <tr> <td>December</td> <td>1985</td> </tr> </table>	MONTH	YEAR	December	1985																	
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5. AUTHOR(S) M. Cristy and R. W. Leggett		6. DATE REPORT ISSUED <table border="1" style="width: 100%; text-align: center;"> <tr> <td>MONTH</td> <td>YEAR</td> </tr> <tr> <td>February</td> <td>1986</td> </tr> </table>	MONTH	YEAR	February	1986																	
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7. PERFORMING ORGANIZATION NAME AND MAILING ADDRESS (Include Zip Code) Health and Safety Research Division Oak Ridge National Laboratory P. O. Box X Oak Ridge, TN 37831		8. PROJECT/TASK/WORK UNIT NUMBER																					
10. SPONSORING ORGANIZATION NAME AND MAILING ADDRESS (Include Zip Code) Division of Waste Management Office of Nuclear Material Safety and Safeguards U.S. Nuclear Regulatory Commission Washington, D.C. 20555		9. PIN OR GRANT NUMBER B0289																					
12. SUPPLEMENTARY NOTES		11a. TYPE OF REPORT Topical																					
13. ABSTRACT <p>This report and a previous one (NUREG/CR-3572) evaluate the dependence or chemical forms of estimates of health effects in high-level waste (HLW). As in the previous report, it is assumed that the organ dose is a suitable index for health effects from exposure to radionuclides, and our discussion is usually directed toward the metabolism and dosimetry of various chemical forms of a radionuclide rather than toward health effects per se. This study is needed because the chemical species of radioelements released to the environment from a high-level waste repository may not be adequately described by the metabolic and dosimetric models of Publication 30 of the International Commission on Radiological Protection. Our previous report dealt with two main topics: (1) identifying those chemical forms of radionuclides which are likely to reach humans after migration from a waste repository and (2) identifying those aspects of the body's metabolism that depend upon the chemical form.</p> <p>It was pointed out in the previous report that one of the greatest uncertainties now present in estimating organ doses from given environmental exposures to various chemical forms of radionuclides lies in the estimate of the fraction absorbed through the gastrointestinal tract to blood. This report deals with two topics on absorption through the gastrointestinal tract: (1) an upper bound for the absorption fraction of plutonium for adults, which is based on data from adult humans, is derived; and (2) the important topic of absorption of radionuclides (strontium and actinides) by neonates and juveniles is reviewed, and a table of recommended absorption fractions for neonates, infants, children, and adults is presented.</p>		b. PERIOD COVERED (Inclusive dates)																					
14. DOCUMENT ANALYSIS -- a. KEYWORDS/DESCRIPTORS <table style="width: 100%;"> <tr> <td style="width: 33%;">GI tract development</td> <td style="width: 33%;">organ dose</td> <td style="width: 33%;">lead</td> </tr> <tr> <td>gastrointestinal absorption</td> <td>metabolism</td> <td>neptunium</td> </tr> <tr> <td>age-dependence</td> <td>americium</td> <td>plutonium</td> </tr> <tr> <td>high-level waste</td> <td>californium</td> <td>protactinium</td> </tr> <tr> <td>waste repository</td> <td>curium</td> <td>strontium</td> </tr> <tr> <td>chemical form</td> <td>einsteinium</td> <td>thorium</td> </tr> <tr> <td>health effects</td> <td>iron</td> <td>uranium</td> </tr> </table>		GI tract development	organ dose	lead	gastrointestinal absorption	metabolism	neptunium	age-dependence	americium	plutonium	high-level waste	californium	protactinium	waste repository	curium	strontium	chemical form	einsteinium	thorium	health effects	iron	uranium	15. AVAILABILITY STATEMENT Unlimited 16. SECURITY CLASSIFICATION <i>(This page)</i> Unclassified <i>(This report)</i> Unclassified 17. NUMBER OF PAGES 18. PRICE
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