EIR-Bericht Nr. 509

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Gastrointestinal Absorption of Actinides: A Review with Special Reference to Primate Data

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Würenlingen, Januar 1964

EIR - BERICHT 509

GASTROINTESTINAL ABSORPTION OF ACTINIDES:

A REVIEW WITH SPECIAL REFERENCE TO PRIMATE DATA

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ABSTRACT

Large scale geological burial of transuranic wastes from fission power production may expose segments of future generations to trace amounts of actinides in water and food, which, via gastrointestinal absorption, could result in internal doses of alpha radiation. Gastrointestinal absorption of actinide elements is a poorly understood process. Experimental studies, primarily using rodents, often produce ambiguous results with order of magnitude fluctuations in estimates of GI absorption. Since experimental conditions like the chemical form of the fed actinides or reducing and complexing capacity of the stomach content, influence the GI transfer factor in seemingly unpredictable ways, only a better understanding of events at the molecular level will enable more reliable predictions to be made of the organ burdens resulting from actinides passing through the digestive tract. From a review of the existing literature it is apparent that in vitro research data in the area of GI uptake mechanisms (i.e. transport mediated by ion carriers in body fluids and across cell membranes) are virtually non-existant.

In view of the uncertainties linked to in vivo uptake experiment, models which approximate man, i.e. derived from non-human primate studies, should be the best choice of experimental systems in which to determine reliable estimates for gastrointestinal transfer factors of actinide elements.

INTRODUCTION

The family of the actinides contains only two naturally occurring elements in abundance: thorium and uranium. Despite the ubiquitous presence of these elements in soil and sea, their use in human activities was very limited until the onset of fission power in military and civil applications. Although these natural actinides are radioactive, their long half lives of billions of years results in very low specific activities. Therefore, their chemical toxicity often becomes the limiting factor in health risk assessments.

Neutron capture by actinides, on a large scale in fission reactions, and beta decay of the resulting nuclides lead to a whole array of unstable transuranium elements with quite unique chemical and biological behaviour. Due to the large energies involved in their alpha decay modes and their very long effective half lives, extremly low limits have been set for occupational and environmental exposures.

Since, thus far, only workers in specialized nuclear facilities were at risk of incorporating significant amounts of the transuranium nuclides (usually via accidental inhalation or wounds) studies on the biokinetics of the actinide elements have emphasized incorporation via the air path or, as a model for wounds or tissue distributions, intravenious injections. The large inventory of the transuranic actinides currently building up at power reactors will be stored in a manner which is being designed to exclude the possibility of inhalation for very long time periods. Consequently, the critical pathway to the human environment will be through ground water by the contamination of drinking water and food. Hence, determination of the transfer factors

for the gastrointestinal absorption of actinides under environmental conditions becomes essential. Transfer factors across the GI tract (f1) , traditionally used in radiological protection to estimate committed radiological doses, range from 5 x 10-2 for uranium to 10-5 for insoluble plutonium (ICRP78). Recent considerations like the possibilities of higher uptake in newborn mammals (Su75) or complex formation of actinide trace quantities with humic acids under environmental conditions leading to higher mobility and solubility, make it necessary to reassess these values for all possible critical populations.

The highly charged ions of the actinide elements lead to very long biological half lives especially in bony structures and the liver. Therefore, a quantitative assessment of the consequences of actinide exposure in man must be based on an animal model with metabolic parameters in the tissues of concern which are comparable to human values. Unfortunately, most rodents i.e. rats, mice and hamsters do not fulfill this prerequisite. Animal orders (species) that are considered more suited for this kind of study are the canine (beagle dog) and the non-human primates eg baboon and eynamologous monkey. The longlivedness and the close phylogenetic relationship of the last category make the primate order an especially desirable experimental model. On the other hand, the scarcity of some primates and the high treatment and maintenance costs, relegate experiments with primates like the baboon to a relatively limited number of study parameters.

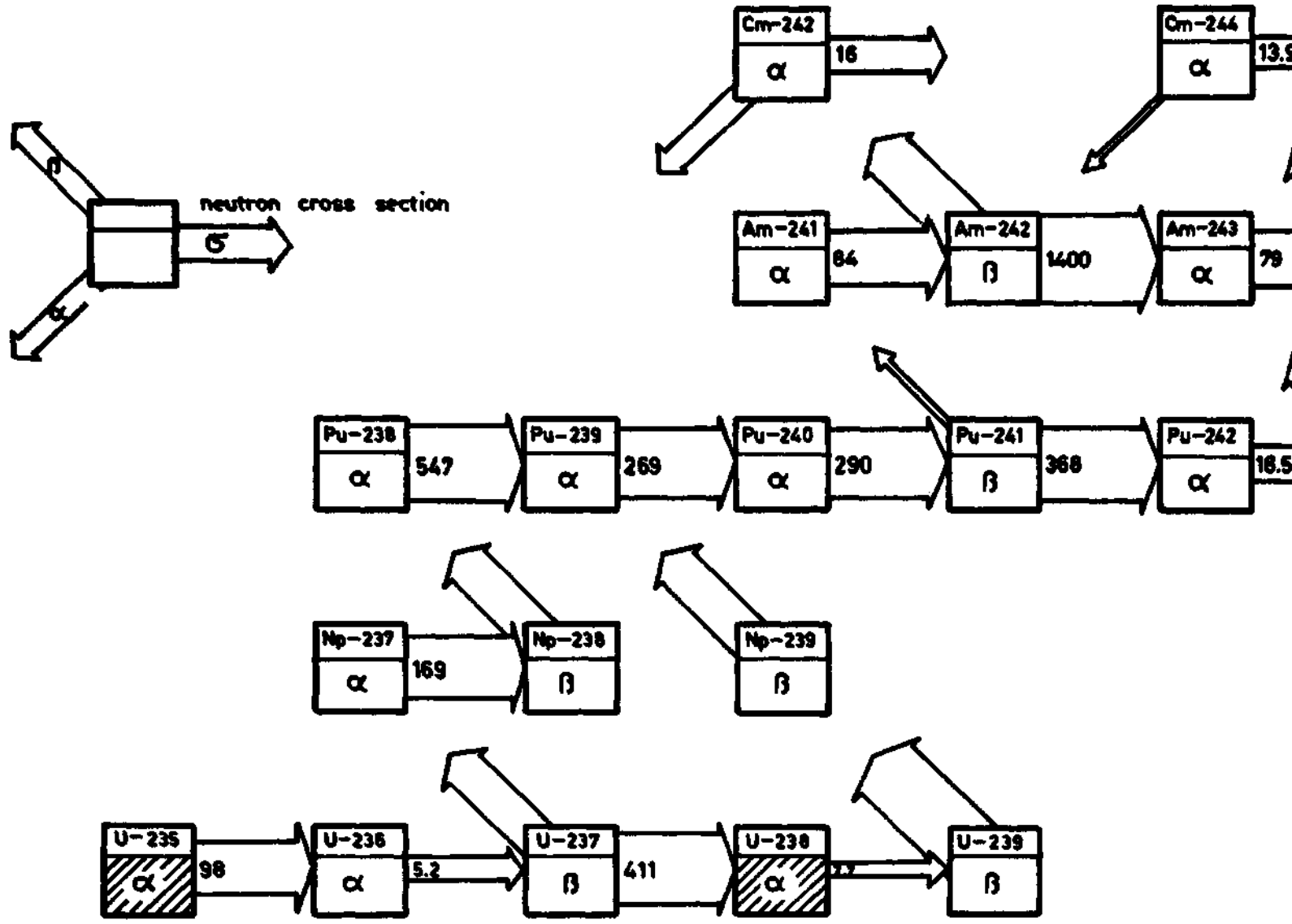
II ACTINIDES IN BIOLOGICAL SYSTEMS

II.1 Physical and Chemical Properties

Uranium and thorium are the primary fuel of modern day nuclear power reactors. The other actinides are produced in reactors by neutron capture in the fuel followed by beta decay. Figure 1 gives an overview on the major production pathways for the long-lived, artificially produced transuranium nuclides. Specific applications of these elements include use as fissionable material in power reactors (Pu-239), as fuel cell power sources (Pu-238) and as alpha sources in commercial products eg in smoke detectors (Am-241). Since, with the exception of plutonium-239, production by far exceeds industrial consumption, most of the longlived transuranium elements will have to be stored in committed high level radioactive waste repositories.

Although far over a hundred actinide nuclides have been identified, only a small fraction of them are of any biological interest either as a result of their long half-lives or of their significant production rates in power or military reactors. Figure 1 shows the most important

Figure 1: Actinide nuclides of importance in the fuel cycle of uranium fission reactors.
The thickness of the arrows for neutron capture and for alpha or beta decay corresponds to the logarithm of the neutron cross section and of the decay constants, respectively. Only decays with a half-live shorter than 70 years (lambda smaller than 0.01 a-1) are shown. Hatched boxes: primordial nuclides.


neutron cross section
σ
Cm-242
α
16
Cm-244
α
Am-241
α
84
Am-242
β
1400
Am-243
α
Pu-238
α
547
Pu-239
α
269
Pu-240
α
290
Pu-241
β
368
Pu-242
α
Np-237
α
169
Np-238
β
Np-239
β
U-235
α
98
U-236
α
5.2
U-237
β
411
U-238
α
U-239
β

production pathways in uranium fission reactors and decay mode of the shorter lived nuclides. Table I gives the most important isotopes for the different elements, their decay energy and decay mode (which is predominantely by alpha emission for the longer half-lives) and X-rays important in their in vitro detection in man after biological incorporation.

Table I: Nuclear properties of the major actinide nuclides

Isotop	half-live a-1	decay mode, MeV	γ,X-rays keV, %	specific activity MBq/g (Ci/g)	source/use
Actinium					
Ac-227	2.18E01	b,0.04 a,4.954	100, 84	2.68E06 (7.24E01)	natural, from U-235
Ac-228	7.00E-4	b,1.2 2.1 a,4.27	911,969 338,965	8.30E10 (2.24E06)	n,γ from Ac-227
Thorium					
Th-228	1.91E00	a,5.423 5.340	84	3.06E07 (8.26E02)	
Th-229	7.34E03	a,4.845 4.901 4.815	194 34 211	7.88E03 (2.13E-1)	
Th-230	7.54E04	a,4.688 4.621	68 144	7.22E02 (1.95E-2)	natural, from U-235
Th-232	1.41E10	a,4.013 3.954	59	4.11E-3 (1.11E-7)	primordial/ U-233 breeding
Th-233	4.24E-5	b,1.2	87, 29 459	1.34E12 (3.63E07)	from Th-232/ U-233 breeding

Isotop	half-live a-1	decay mode, MeV	γ,X-rays keV, %	specific activity MBq/g (Ci/g)	source/use
Th-234	6.60E-2	b,0.2	92, 63	8.58E08 (2.32E04)	natural, from U-238
Protactinium					
Pa-231	3.28E04	a,5.014 4.952 5.028	27 303 300	1.68E03 (4.53E-2)	natural, from U-235 decay
Pa-233	7.40E-2	b,0.3 0.6	312 300,341	7.59E08 (2.05E04)	from Np-237 decay
Pa-234	7.65E-4	b,0.5 1.2	131 881,883	7.40E10 (2.00E06)	natural from U-238 decay
Uranium					
U-233	1.59E05	a,4.824 4.783	(42) (97)	3.51E02 (9.48E-3)	from Th-232/ reactor fuel
U-234	2.45E05	a,4.775 4.723	(53) (121)	2.28E02 (6.17E-3)	natural, from U-238
U-235	7.04E08	a,4.400	186	7.92E-2 (2.14E-6)	primordial/ reactor fuel
U-236	2.34E07	a,4.494 4.445	(49) (113)	2.35E00 (6.35E-5)	n,γ from U-235
U-237	1.85E-2	b,0.2	60 208	3.02E09 (8.17E04)	n,γ from U-236
U-238	4.47E09	a,4.197	(50)	1.23E-2 (3.33E-7)	primordial/ Pu-239 breeding
U-239	4.47E-5	b,1.2 1.3	75 44	1.24E12 (3.35E07)	n,γ from U-238/ Pu-breeding

Isotop	half-live a-1	decay mode, MeV	γ,X-rays keV, %	specific activity MBq/g (Ci/g)	source/use
Neptunium					
Np-237	2.14E06	a,4.788 4.771	29 87	2.61E01 (7.07E-4)	α from Am-241, β from U-237
Np-238	5.80E-3	b,1.2	984,1029 1026,924	9.58E09 (2.59E05)	n,γ from Np-237
Np-239	6.45E-3	b,0.4 0.7	106,278 228	8.69E09 (2.35E05)	β from U-239/ Pu-239 breeding
Plutonium					
Pu-238	8.77E01	a,5.499 5.456	(43) (100)	6.36E05 (1.72E01)	β from Np-238/ heat source
Pu-239	2.42E04	a,5.157 5.144	(52)	2.27E03 (6.13E-2)	β from Np-239/ reactor fuel
Pu-240	6.55E03	a,5.168 5.124	(45)	8.40E03 (2.27E01)	n,γ from Pu-239
Pu-241	1.44E01	a,4.896	(149)	3.67E06 (9.91E01)	n,γ from Pu-240 reactor fuel
Pu-242	3.76E05	a,4.901 4.856	(45)	1.41E02 (3.82E-3)	n,γ from Pu-241
Pu-243	5.66E-4	b,0.6	84	9.62E10 (2.60E06)	n,γ from Pu-242
Pu-244	8.26E07	a,4.589 4.546		6.55E-1 (1.77E-5)	n,γ from Pu-243
Americium					
Am-241	4.33E02	a,5.486 5.442	60 26	1.27E05 (3.43E00)	β from Pu-241
Am-242m	1.83E-3	b,0.6 0.7	(42)	2.99E10 (8.09E05)	n,γ from Am-241 reactor fuel

Isotop	half-live a-1	decay mode, MeV	γ,X-rays keV, %	specific activity MBq/g (Ci/g)	source/use
Am-243	7.37E03	a,5.275 5.233	75 44	7.40E03 (2.00E-1)	β from Pu-243, n,γ from Am-242
Am-244	1.15E-3	b,0.4	744,898 154	4.72E10 (1.28E06)	n,γ from Am-243 reactor fuel
Curium					
Cm-242	4.46E-1	a,6.113 6.069	(44)	1.23E08 (3.32E03)	β from Am-242
Cm-244	1.81E01	a,5.805 5.763	(43)	2.99E06 (8.09E01)	β from Am-244

Actinides are metals which oxidise readily. Only thorium is quite unreactive in pure form. In finely divided form uranium and all higher actinides may be pyrophoric. Table II lists some important chemical features. The small diameter of the ions which is due to the filling of inner shells combined with the high charges are responsible for the unique chemical and biological behavior of the actinides. Outside the laboratory only few compounds are stable. In the environment, oxides, hydroxides and complexes with organic materials like humic and fulvic acids have to be considered.

In the environment, several factors may lead to an increase in one or more transport factors. In addition to the natural organic complexes already mentionned, changes in the redox state due to chlorination (La78) or due to seasonally anoxic lake waters (Sh82) and high affinity binding to the exoskeleton of water microorganisms were shown to influence the behaviour of actinides in the food web drastically. Actinide oxide particles dissolve very slowly under

physiological conditions; therefore, the surface/mass ratio i. e. particle size and the temperature at which the particles were calcined become important parameters for the estimation of biological uptake.

Table II: Physical and chemical properties of the actinides

Element	melting point (C)	Oxidation state *	ionic radii (A) ** (Wh70)	ligand	complex constants logK1 (I / T) (Ma76)
Actinium	1050	3		fluoride	2.72 (0.5/25)
				sulfate	1.20 (1.0/25)
				oxalate	4.36 (0.1/25)
Thorium	1750	4	1.08 (VI)	fluoride	7.59 (0.5/25)
			1.12 (VIII)	sulfate	3.22 (0.5/25)
			1.17 (IX)	citrate	13.0 (0.5/25)
				dicitrate	21.0(logBC)
				DTPA	28.78 (0.1/20)
				EDTA	23.2 (0.1/20)
				oxalate	8.8 (0.1/25)
		3			
Protactinium	1230	5	0.99 (VIII)	fluoride	3.56 (1.0/25)
		4	1.09 (VIII)	fluoride	8.03 (1.0/25)
Uranium	1132	6	0.53 (II)	EDTA	7.36 (0.1/20)
		(UO2,2+)	0.81 (VI)	oxalate	6.36 (0.1/25)
		5	0.84 (VI)		
		4	1.06 (VII)	fluoride	9.0 (0.0/25)
			1.08 (VIII)	sulfate	3.42 (0.5/25)
			1.13 (IX)	citrate	11.8 (0.5/25)
				dicitrate	19.5(logB2)
				DTPA	7.69 (0.1/20)

Element	melting point (C)	Oxidation state *	ionic radii (A)	ligand	complex constants logK1 (I / T)
(Uranium continued)		4		EDTA	25.8 (0.1/20)
		3	1.12 (VI)		
Neptunium	637	6			
		5 (NpO2,1+)		EDTA	7.33 (0.1/25)
				oxalate	6.36 (0.1/25)
		4	1.06 (VIII)	fluoride	8.3 (0.0/25)
				sulfate	3.51 (0.5/25)
				DTPA	30.3 (1.0/20)
				EDTA	24.6 (0.0/20)
		3	1.10 (VI)		
Plutonium	640	6 (PuO2,2+)		oxalate	9.4 (1.0/25)
		5 (PuO2,1+)		EDTA	4.8 (0.1/25)
		4	0.88 (VI)	fluoride	6.77 (1.0/25)
			1.04 (VIII)	sulfate	3.66 (1.0/25)
				citrate	15.2 (0.5/25)
				dicitrate	29.5(logB2)
		3	1.09 (VI)		
Americium		6			
		5			
		4	1.03 (VIII)		
		3	1.08 (VI)	fluoride	3.39 (0.5/25)
				sulfate	1.86 (0.5/25)
				citrate	7.74 (0.1/25)
				DTPA	22.9 (0.1/25)
				EDTA	17.8 (0.1/25)
				oxalate	5.25 (0.1/25)
Curium		4	1.3 (VIII)		
		3	1.06 (VI)	fluoride	3.34 (0.5/25)

Element	melting point (C)	Oxidation state *	ionic radii (A)	ligand	complex constants logK1 (I / T)
(Curium continued)		3		sulfate	1.86 (0.5/25)
				DTPA	23.0 (0.1/25)
				EDTA	18.1 (0.1/25)
				oxalate	5.25 (0.1/25)
Einsteinium		3		DTPA	22.6 (0.1/25)

* Most common state in the environment is underlined

** Strictly appropriate only to bonding of cations to O and F. Roman numerals denote co-ordination number.

II.2. Principles of Gastrointestinal Absorption

All ingested material and a significant percentage of the inhaled actinide activity will enter the gastrointestinal tract. Although this system is specialized to break down food through enzymatic action, pH-changes and solubilization to facilitate uptake of the resulting small molecules and ions into the blood stream and the lymph through active transport and diffusion, the unique chemical behaviour of most actinide elements generally results in extremly low systemic uptake values (see Table III and Section III).

For charged ions of the actinide series several uptake mechanisms characteristic of the gastrointestinal system may be of importance:

1) Solubilization resulting from the low pH of the stomach or from food constituents having the capability to

chelate polyvalent ions, e.g. the low pH of about 1 in the stomach may theoretically help to dissolve particulate actinide oxides or hydroxides. Very powerful natural chelating agents such as polycarboxylic acids (citric acid, oxalic acid) are usually present in our diet. Quite recently, Cooper and Harrison (Co82) identified phytate (myo-inositol hexakisphosphate), a constituent of potato, as an important plutonium-binding species. Concentrations in food stuff may be quite high, i.e. 1.4 mM phytate (26 mg of phosphorous per 100 g) and 17 mM citrate in potato julce (Co82).

2) Specialized active transport systems for polyvalent ions such as calcium or iron may display a certain affinity towards other elements as well. Indirect evidence is provided by the high affinity of plutonium and americium to the iron binding protein transferrin. A large body of literature describes the active transport process for iron by duodenal and jejunal mucosa (Co80, Mar79). It is also suggested that mitochondria of brush border cells are actively implicated in the intestinal transport of iron (Ho79).

3) Uptake by pinocytosis (internalization of patches of the cell membrane with adhering extracellular material by formation of internal vesicles from the surface membrane). This mechanism could play a role in neonatals, in which uptake of macromolecules (maternal antibodies) is well established (Bu82). However, permeability of the intestinal linings to large molecules for some days after birth could also account for the elevated transfer factors of newborn mammals.

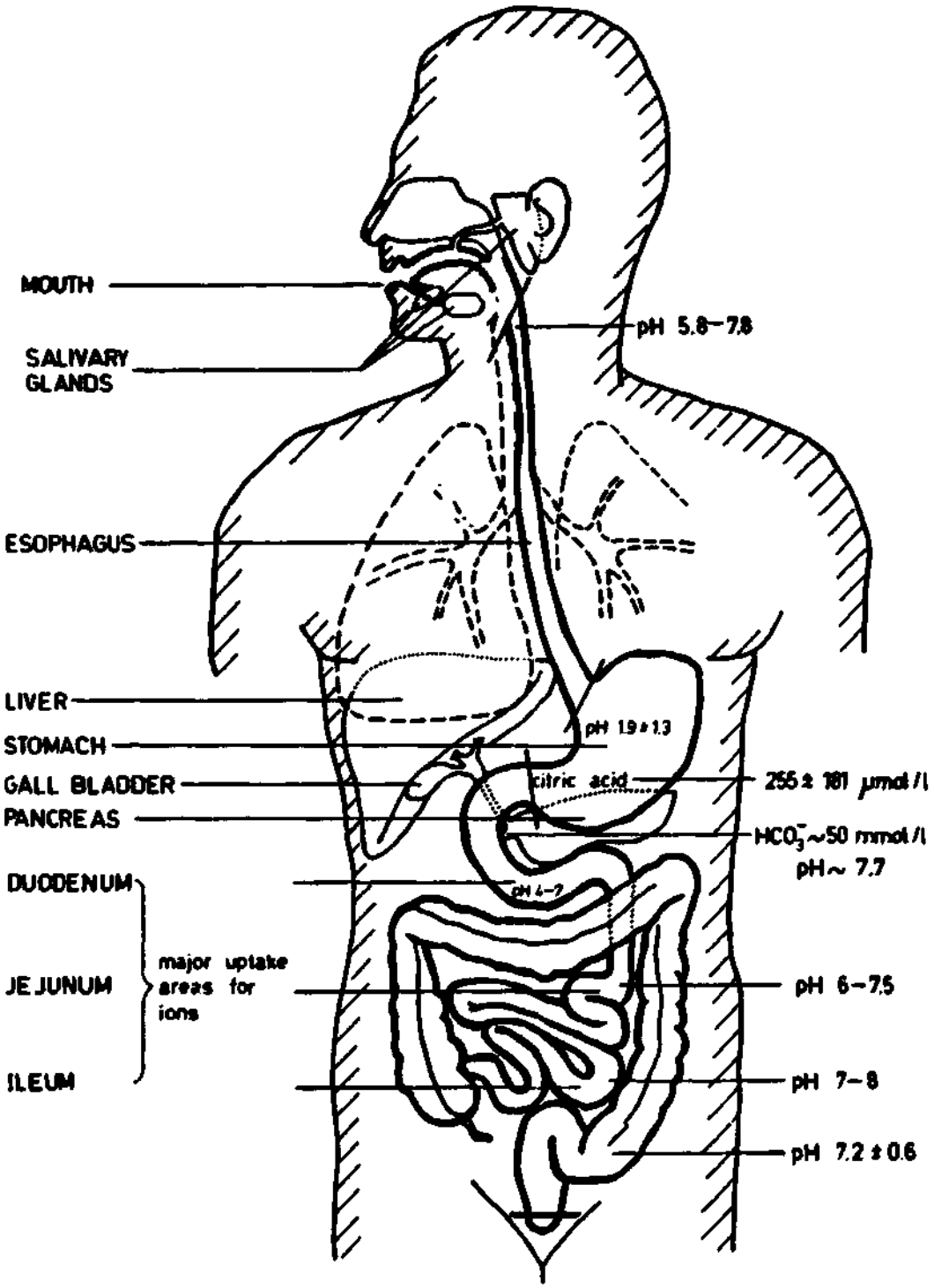
4) It has been suggested that phospholipids present in the cell membrane could act as ionophores to facilitate undirected transmembrane transport. Bulman et al (Bu77) showed that thioacetamide intoxication which icreases hepatic acidic phospholipid levels, resulted in an enhancement in the uptake of plutonium into rat liver. More recently, a specific lipid, phosphatydilserine, was implied in the transport of plutonium,

americium and curium (Bu80). Protactinium is neither complexed by this phospholipid nor taken up by the liver to any considerable amount.

In addition, individual differences may be introduced by endogenous intestinal factors which influence mucosal uptake: oxidation state of the actinide, mass of actinide, nutritional status i.e. fasted or fed, gastric and intestinal secretions and the state of the brush border of the mucosal cells (Mar79).

Figure 2 shows schematically the changes an actinide may undergo in the different compartments of the gastrointestinal tract. In the human, the small intestine with its three levels of folds (valvulae conniventes, villi, microvilli) presents a total surface area of about 250 square meters to the passing chyme and therefore, acts as the main absorbing organ of the gastrointestinal tract. Fifty to 100 grams of ions, mostly mono- and divalent, are absorbed in this area per day.

Figure 2: Schematic representation of gastrointestinal uptake for ions. Only organs, substances and values of relevance for actinide complexation and transport are shown (data base from Ci77, Gu77).


MOUTH
SALIVARY GLANDS
ESOPHAGUS
LIVER
STOMACH
GALL BLADDER
PANCREAS
DUODENUM
JEJUNUM
ILEUM
major uptake areas for ions
pH 5.8–7.8
pH 1.9 ± 1.3
citric acid
255 ± 181 µmol/l
HCO_3^- ~50 mmol/l
pH ~ 7.7
pH 4–7
pH 6–7.5
pH 7–8
pH 7.2 ± 0.6

II.3. Human and Nonhuman Primate Metabolism Data

Only few months after the first transuranium element plutonium became available this element was injected into terminally ill human subjects to investigate its behaviour in biological systems (La50). The long biological half-lives found in this study made it unethical to proceed with human studies. Besides uranium and thorium which where taken up by humans during medical treatment (thorotrast) or due to occupational exposure, direct measurements of the biokinetic behaviour of the actinides in man is limited to the assessment of accidental incorporations in a few laboratories and reprocessing plants handling such elements. Today, the radiological protection standards are such that measurable internal contamination is virtually absent. In the few cases with high enough activities taken up to allow follow up measurements, therapies like chelation or lung lavage may influence the excretion patterns in an unpredictable way. In most of the cases, the pathways for accidental incorporations are inhalation or wound contamination of hand and forearm. Although inhalation results in the transfer of a large amount of the activity into the gastrointestinal tract by mucociliary transport, the concomitant transfer to the blood directly in the lung or via the lymphatic system does not allow the estimation of gastrointestinal absorption from inhalation cases.

In this situation, experiments with nonhuman primates offer an opportunity to measure the longterm behaviour of actinide elements after ingestion or i.v. injection. Comparisons of the exretion patterns found in such controlled experiments with the scarce human data from accidental incorporations show good agreement (Co83). However, since most

of the animal experiments were undertaken to evaluate accidental inhalation or uptake through wounds, relatively few data exists on the gastrointestinal uptake route.

From in vitro work it was found that shortly after intravenous injection, the actinide ions become bound to macromolecules in the blood. Plutonium binds to the iron transporting protein transferrin, a beta 1 globulin, with quite high affinity. Since an excess of iron displaces plutonium and, as for iron, bicarbonate ions are needed as cofactor, it is assumed that similar binding sites are involved (Tu68). Binding occurs during the first minute after injection of a soluble complex and it is assumed that 99.99 % of the plutonium in human blood is bound to transferrin (Ta81). The same group found also evidence for the binding of thorium and americium to the same protein. Other proteins which bind di- and trivalent metal ions could also act as carriers in the blood and may influence the time course of the transfer of the activity to the organs of deposition. Studies at New York University Medical Center on baboon indicate that protactinium, which shows the slowest transfer from the blood compartment, has a relative affinity to blood components about two orders of magnitude higher than americium and curium (Co83). In the case of metallothionein, a plasma carrier for metals like zinc, cadmium, copper and mercury, it was shown that metal poisoning increases the carrier concentration in the plasma (Ga81).

Specific binding is of decisive importance for the distribution of the activity to the different organs. Since the liver is a storage site for iron, liver cells display transferrin receptors on their surface which lead to a prefferential uptake of any metal bound to transferrin into hepatocytes (Ai80). Human lymphoblasts containing transferrin receptors were shown to take up 20 times more plutonium and 4 times more americium than receptor deficient cells (Ta81). It is evident that distribution mechanisms relying on cell

surface receptor densities on cells of the immune system will show large differences between individuals of the same species. Large interspecies differences have to be expected.

II.4. Nonprimate Studies

For the lower actinides up to americium and especially for plutonium, there exists a large body of data on the biokinetics of different chemical forms of the elements and on chelation therapies reducing biological half-lives. These studies have resulted in considerable information for events at the molecular, subcellular and cellular level. Carrier proteins in the body fluids, subcellular locations and the long term behaviour in the bone matrix are quite well defined. Such progress opens the door to efficient treatments to reduce the radiation dose after high exposures. The major shortcomings of the most frequently employed rodent systems are in the short life span of the animals (which does not allow the expression of late effects) and in short tissue turnover times. The beagle dog studies overcome some of these limitations. It is widely used for inhalation and i.v. studies but the feeding requirements of the canine (carniverous versus omniverous for most primates) make it a poor model for ingestion.

Ingestion studies with newborn animals indicate that neonates have a much larger gastrointestinal uptake of actinides than adult animals (Su75, Su82). This may be caused by the permeability of the digestive tract of newborns to macromolecules or even to active uptake processes like pinocytosis of the intestinal epithelium. Such mechanisms are probably involved in many species in the transfer of antibodies from mother to offspring via milk during lactation.

II.5. The ICRP Model

Due to a lack of appropiate human or primate studies, many limits of the "International Commission on Radiological Protection" are based on scant information obtained using less than optimal experimental designs and reflect conservative dose expectations but not necessarily a best scientific estimate. Figure 3 shows schematically the major pathways of plutonium in the human body using ICRP data (ICRP78).

Organ sizes and weights used in the ICRP estimations are from a "Reference Man" (ICRP75), lung deposition and biological half-lives from ICRP 30 (ICRP78). Table III shows gastrointestinal uptake as assumed by ICRP and expressed as fraction of the ingested activity. The values range from 0.01 to 10-5. In Chapter III, these estimates are compared to the data base for each element.

Figure 3: Body compartments, relative distribution to subcompartments in % and half-lives of transfer for insoluble plutonium (oxide or hydroxide) in the ICRP Reference Man

- number in parenthesis in hatched area denote fractions of inhaled activity retained in the different areas of the respiratory tract for particles with a diameter of 1 um.
- compartments of the respiratory tract: N-P naseo-pharyngeal (a,b)
  T-B tracheo-bronchial (c,d)
  P pulmonary (e,f,g,h)
  lung lymph nodes (i,j)

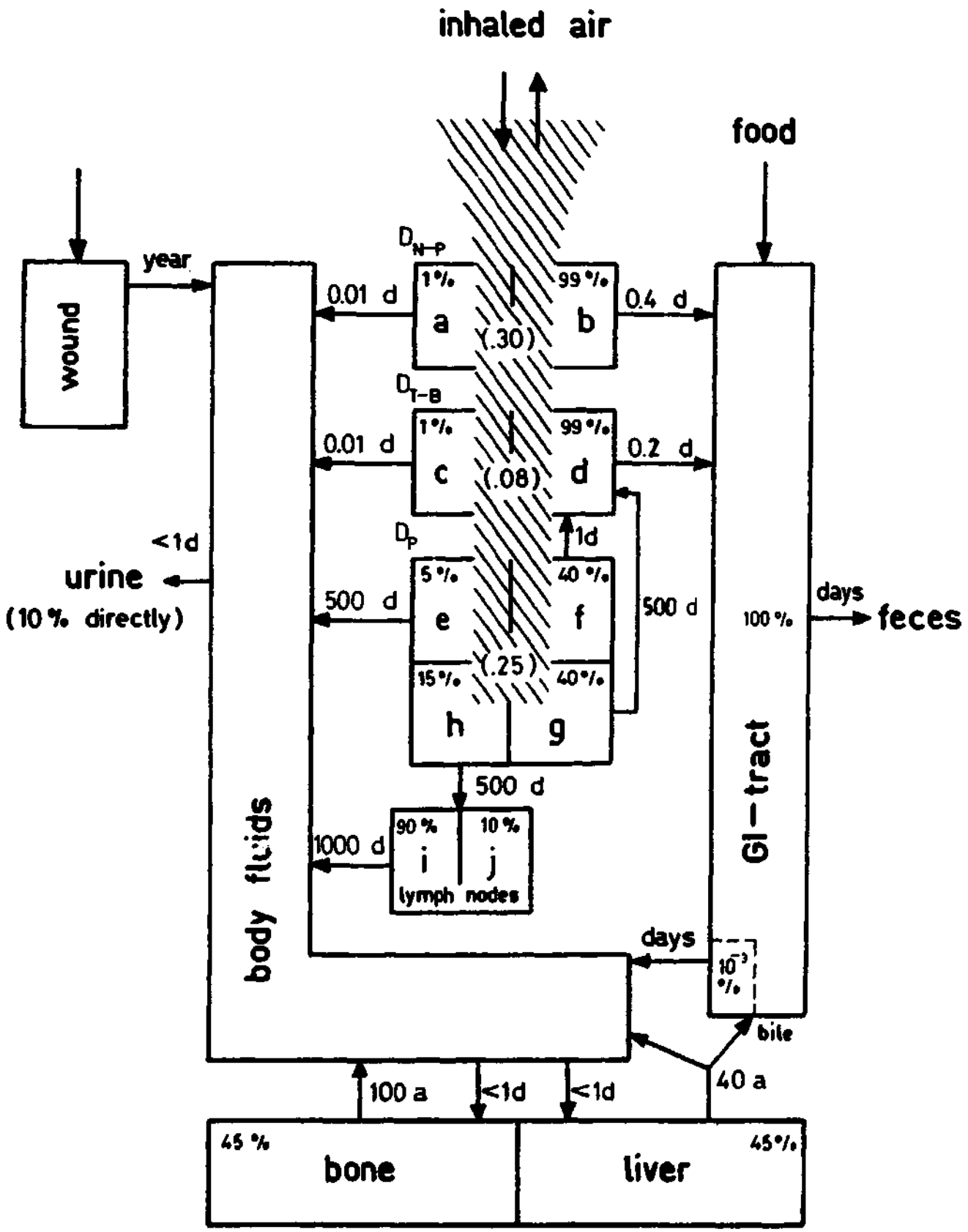

inhaled air
food
wound
year
D_{N-P}
1 %
99 %
a
(.30)
b
0.01 d
0.4 d
D_{T-B}
1 %
99 %
c
(.08)
d
0.01 d
0.2 d
1d
D_P
5 %
40 %
e
f
500 d
500 d
15 %
40 %
h
g
500 d
90 %
10 %
i
j
lymph nodes
1000 d
<1d
urine
(10 % directly)
days
100 %
feces
GI-tract
body fluids
days
10^{-3} %
bile
100 a
<1d
<1d
40 a
45 %
bone
liver
45 %

Table III: ICRP values for gastrointestinal uptake in the human for actinide elements (ICRP78). ALI: annual limit of oral intake (occupational exposure limit)

Element	chemical form	fractional uptake	ALI in Bq	(nuclide)
actinium	all compounds	10-3	7.0E03	Ac-226
	*		9.0E07	Ac-227
thorium	" "	2 x 10-4	2.0E05	Th-228
			2.0E04	Th-229
			1.0E05	Th-230
			3.0E04	Th-232
protactinium	" "	10-3	7.0E03	Pa-231
			5.0E07	Pa-233
			9.0E07	Pa-234
uranium	hexavalent,	5 x 10-2	5.0E05	U-235
	inorganic		5.0E05	U-236
			5.0E05	U-238
			2.0E09	U-239
	UF4, UO2, U3O8	2 x 10-3	7.0E06	U-235
			8.0E06	U-236
			8.0E06	U-238
			2.0E09	U-239
neptunium	all forms	10-2	3.0E03	Np-237
			6.0E07	Np-239
plutonium	oxides,	10-5	3.0E06	Pu-238
	hydroxides		2.0E06	Pu-239
			2.0E06	Pu-240
			1.0E08	Pu-241
	other forms	10-4	3.0E05	Pu-238

Element	chemical form	fractional uptake	ALI in Bq	(nuclide)
(plutonium continued)		10-4	2.0E05	Pu-239
			2.0E05	Pu-240
			1.0E07	Pu-241
americium	all forms	5 x 10-4	5.0E04	Am-241
			5.0E04	Am-243
curium	all forms	5 x 10-4	2.0E06	Cm-242
			9.0E04	Cm-244
higher actinides	all forms	5 x 10-4		

* complexing agents not taken into account

II.6. Chemotoxicity of Actinides

The unique chemical characteristics of the actinides which lead to the long residence time in human tissues may also produce toxic effects on enzymes and renal structures. Therefore, the chemotoxic effects of longlived nuclides may be the limiting factor. This holds for the primordial nuclides U-238, U-235 and Th-232. However, for plutonium-239 with a half-live of 24'200 years and all shorter-lived actinide nuclides, chemotoxic effects as compared to the radiological risk can be neglected.

Table IV: Biokinetics of actinides. Body distribution expressed as organ burdens in % of activity entering the blood; The activity not accounted for is presumed to be excreted directly. Biological half-lives in parenthesis. (After ICRP78)

	mineral bone	liver	kidney	gonads	others
Actinium	45 (100 a)	45 (40 a)		m .03 (∞) f .01 (∞)	
Thorium	70 (8000 d)	4 (700 d)			16 (700 d)
Protactinium	40 (100 a)	10.5 (10 d) 4.5 (60 d)	0.4 (10 d) 1.6 (60 d)		
Uranium	20 (20 d) 2.3 (5000 d)		12 (6 d) 0.05 (1500 d)		12 (6 d) 0.05 (4 a)
Neptunium	45 (100 a)	45 (40 a)		m .03 (∞) f .01 (∞)	
Plutonium	45 (100 a)	45 (40 a)		m .03 (∞) f .01 (∞)	
Americium and all the higher actinides are assumed to behave like plutonium					

III SPECIFIC NUCLIDES

III.1. The naturally occuring actinides: thorium and uranium

Thorium and uranium are ubiquitous constituents of our environment and of our food. Although through their decay products they contribute the largest segment to the natural background radiation, their direct dose contribution is small. Both elements are taken up in measurable quantities by the general population. Daily intake in food and fluids is estimated at 3 µg for thorium and 1.9 µg for uranium (Reference Man, ICRP 75).

From four hospital patients given uranyl nitrate orally, total absorption of soluble uranium was estimated at between 0.5 and 5 % (Hu69). The fractional absorption of both elements was found to be quite low for occupational exposures. Table IV shows data from animal experiments and the value adopted by ICRP. As with all the following elements, gavage of neonatal animals with uranium nitrate leads to transfer of up to 31 % of the activity to the skeleton (Su82). However, in the light of experimental data accrued with adult animals, the ICRP absorption factors seem to be conservative. A value of 1 % is considered more realistic for soluble hexavalent forms (Ha81).

As already noted, for the primordial nuclides, the chemical toxicity of thorium and uranium is the limiting factor for organ burdens. The proximal convoluted tubules of the kidney show the first structural changes due to the heavy metal toxicity of uranium. Functional studies describe proteinuria and shifts in the clearance pattern of substances like glucose

and amino acids which are normally reabsorbed in the convoluted tubules (St82). Possible molecular events leading to these effects are the precipitation of uranium compounds in the kidney and inactivation of enzyme systems.

Table IV: Absorption of thorium and uranium in the gastrointestinal tract

Organism	chemical form	fractional absorption	Ref.
Thorium			
man	Th(SO4)2	10-4 - 6 x 10-4	Ma69
rat	Th(NO3)4	5 x 10-3 - 10-2	Tr70
mouse	Th-228 nitrate	6 x 10-4	Su83a
rat, neonatal	Th-228 nitrate	0.011	Su83a
man (ICRP)	all forms	2 x 10-4	ICRP78
Uranium			
man	UO2(NO3)2.6H20	0.005 - 0.05	Hu69
man	UO2, U3O8	less than 0.01	Yu73
man (environmental level)	oxides	0.2	Hu73
hamster	UO2(NO3)2	0.0077	Ha81
	UO2	0.0011	"
mongrel dog	UO2F2	0.0155	Fi60
swine, neonatal	UO2(NO3)2	0.35	Su82
man (ICRP)	hexavalent, inorganic	0.05	ICRP78
	UF4, UO2, U3O8	0.002	"

An interesting case is the clear relationship between the use of thorotrast, a thorium-232 dioxide-containing contrasting suspension and higher liver cancer incidence in such patients. New theories however, link the cancer induction to the chemotoxicity of thorium and not to the alpha-radiation of thorium-232 (St83).

III.2. Neptunium

Neptunium does not occur naturally and no human data is available at this time. Nevertheless, its long-lived isotope Np-237, which is produced in reactors (from U-237) and also builds up in americium-containing waste through decay of Am-241, may be the critical nuclide for considerations of the disposal of reprocessed fuel from nuclear power plants in the intervall from 10'000 years to 30 million years following disposal (Th82). This is due to its relatively fast transport in geological formations, high transfer factors in food chains (Pr72) and indications that the gastrointestinal uptake is greater than for other transuranium elements. A review of the production and recovery techniques for neptunium indicates the importance of this element in the production of higher actinides (Sc72).

Several studies on the adsorption of neptunium on soil particles showed that the most stable pentavalent form of neptunium is at least one order of magnitude more mobile than americium and curium (Se79).Table V gives the values for fractional uptake in the digestive tract. The range of values found is quite wide and ranges from 0.06 % to 6 % in neonatal swine (Th82, Su82). To approach natural conditions, Sullivan fed 8-day-old rats which had been gavaged with Np-237 to adult

rats (Su76). Fractional transfer in this case was estimated to be around 0.001.

Table V: Absorption of neptunium in the gastrointestinal tract

Organism	chemical form	fractional absorption	Ref.
goat	Np citrate	0.005	Su79
hamster	Np citrate	6 x 10-4	Ha81
	Np nitrate	5 x 10-4	"
rat	Np-237 nitrate	0.012	Th82
	Np-239 nitrate	6 x 10-4	"
	trace quantities	(0.1)	Ba62
	in food	(0.1)	Su75
	Np-237 + ferric nitrate, fasted	0.08	Su83
swine neonatal	Np nitrate	0.06	Su82
man (ICRP)	all forms	0.01	ICRP78

Contrary to the relative behavior of plutonium nuclides with differing half lives, the long-lived Np-237, which is generally fed in much greater amounts on the basis on weight, seems to be taken up to a larger extent than shorter lived neptunium isotopes. Since this effect has been found in several independent studies, it was assumed that chemically induced damage to the digestive tract enhances uptake in the case of the low specific activity nuclides (Co83b).

Recent studies by Sullivan (Su83) brought a quite simple explanation of this phenomenon. At higher concentrations of

the actinide element, the reducing capacity of the digestive tract is not sufficient to convert most of the neptunium from the +V to the +IV state. Since the more oxidized form has a higher uptake probability (Ba62), this change in the oxidation state solves the enigma of concentration dependent fractional transfer. The hypothesis was proven in experimental studies where the reducing capacity of the GI contents was exhausted through the concomittant feeding with ferric iron (Fe+++) in the form of iron nitrate. Total absorption in rats was up to 7.8 % in fasted animals receiving 5 mg/kg neptunium-237 and 70 mg of ferric nitrate (Su83).

The chemical toxicity of Np-237 measured as lethal dose in 3 days (DL50,3), was found to be in the range of 12 to 24 mg/kg in the rat and seems to be even higher in sheep (DL100,3 after administration of 12 mg/kg)(Ne82). Twelve mg Np-237/kg correspond to 310 Bq/g (8.4 nCi/g).

It has to be kept in mind, that sofar, the ICRP value is not based on solid data and should only be used for occupational exposure. It may be that for trace quantities in the environment, the fractional uptake is considerably smaller or greater.

III.3. Plutonium

Although plutonium is an artifical element, measurable quantities are found in food and human tissues from world-wide fallout from nuclear weapons tests. Human data from intraveneous injections (La50) and occupational exposure tend to fit into the very extensive metabolic data from experiments with a multitude of animal species.

Controlled ingestion by humans is not described in the literature. In animal models, gastrointestinal uptake is very low for most plutonium compounds. Some organic complexes without much importance in health physics may show higher fractional uptake values (Table VI). Experiments by Sullivan and Gorham (Su82) show that the actinide mass has a crucial influence on the relative amount absorbed. The short-lived Pu-238 with its much higher specific activity shows a fractional uptake which is 4 times higher than for Pu-239 at a

Table VI: Absorption of plutonium in the gastrointestinal tract

Organism	chemical form	fractional absorption	Ref.
dog, neonatal	Pu-238 oxide	0.002	Su82
hamster	Pu(IV)-236 carbonate	1.3 x 10-5	St81
	Pu(VI)-236 carbonate	1.6 x 10-5	"
	Pu-239 citrate	1.0 x 10-4	"
rat	Pu-238 phytate	1.3 x 10-3	Co82
swine neonatal	Pu(IV) nitrate	0.11	Su82
	Pu(VI) nitrate	0.16	"
	Pu-238 oxide	0.0017	"
	Pu-239 oxide	0.0004	"
man (ICRP)	oxides, hydroxides	10-5	ICRP78
	other commonly occuring compounds	10-4	

dose of about 45 uCi/kg (Su82). This is thought to be caused by the reduced polymerization of Pu-238. Extending this argument to the low environmental levels and different valence states, it was suggested that at very low concentrations, the fractional transfer could be as high as for monomeric

plutonium citrate (La78). Experiments with hamsters which were fed the high specific activity Pu-236 at a concentration of only 10-13 g Pu/l show that these projections are unfounded. Both for Pu(IV) and Pu(VI), absorption from the gastrointestinal tract remained in the range of 10-5 or an order of magnitude below the value for plutonium citrate (St81).

Experiments with neonatal animals again yield an elevated absorption pattern. But at least for plutonium oxide, fractional uptake remains low.

III.4. Americium

Americium can probably be used for more civilian application than any other transuranium element. Am-241 has its widespread use in neutron sources, static eliminators, neutron target and in millions of smoke detectors (Sc76).

Table VII: Absorption of americium in the gastrointestinal tract

Organism	chemical form	fractional absorption	Ref.
rat		10-4 - 0.0014	Mo73
swine neonatal	Am nitrate	0.02	Su82
man (ICRP)	all forms	5 x 10-4	ICRP78

Data on human biokinetics is limited to few investigations

of accidental incorporations (Co79, La73). No cases with ingestion of known activities are reported. Animal data confirm the notion that the behaviour of americium and higher actinides is similar to plutonium. Fractional gastrointestinal uptake in neonatal swine is even lower than for plutonium and lowest of all nuclides tested in this system (Su82). Table VII shows estimates from several experiments.

III.5. Curium

As for all the actinides with Z bigger than 95 (Am), no human data on the gastrointestinal uptake of curium is available. Animal studies led to the recommendation to treat curium like plutonium. The highest value reported was found with neonatal swine. As compared to plutonium given in parallel experiments, gastrointestinal uptake is about three times lower.

Table VIII: Absorption of curium in the gastrointestinal tract

Organism	chemical form	fractional absorption	Ref.
rat		3 x 10-5 - 7 x 10-4	Se73
swine neonatal	Cm nitrate	0.056	Su82
man (ICRP)	all forms	5 x 10-4	ICRP78

III.6. Other Actinides

Of the actinide elements not covered thus far, only actinium and protactinium exist in the environment. Ac-227 with a half-live of 21.77 years is a decay product of uranium-235. Protactinium has 2 nuclides of some importance in radiological protection. Pa-234 and the alpha emitter Pa-231 are members of the U-238 and the U-235 radioactive chains, respectively. Since actinium is not used in human activities, no reports on accidental ingestion were published. Experiments with primates are under way for protactinium (Co83a).

Table IX: Absorption of actinium, protactinium, berkelium, californium, einsteinium, fermium and mendelevium in the gastrointestinal tract

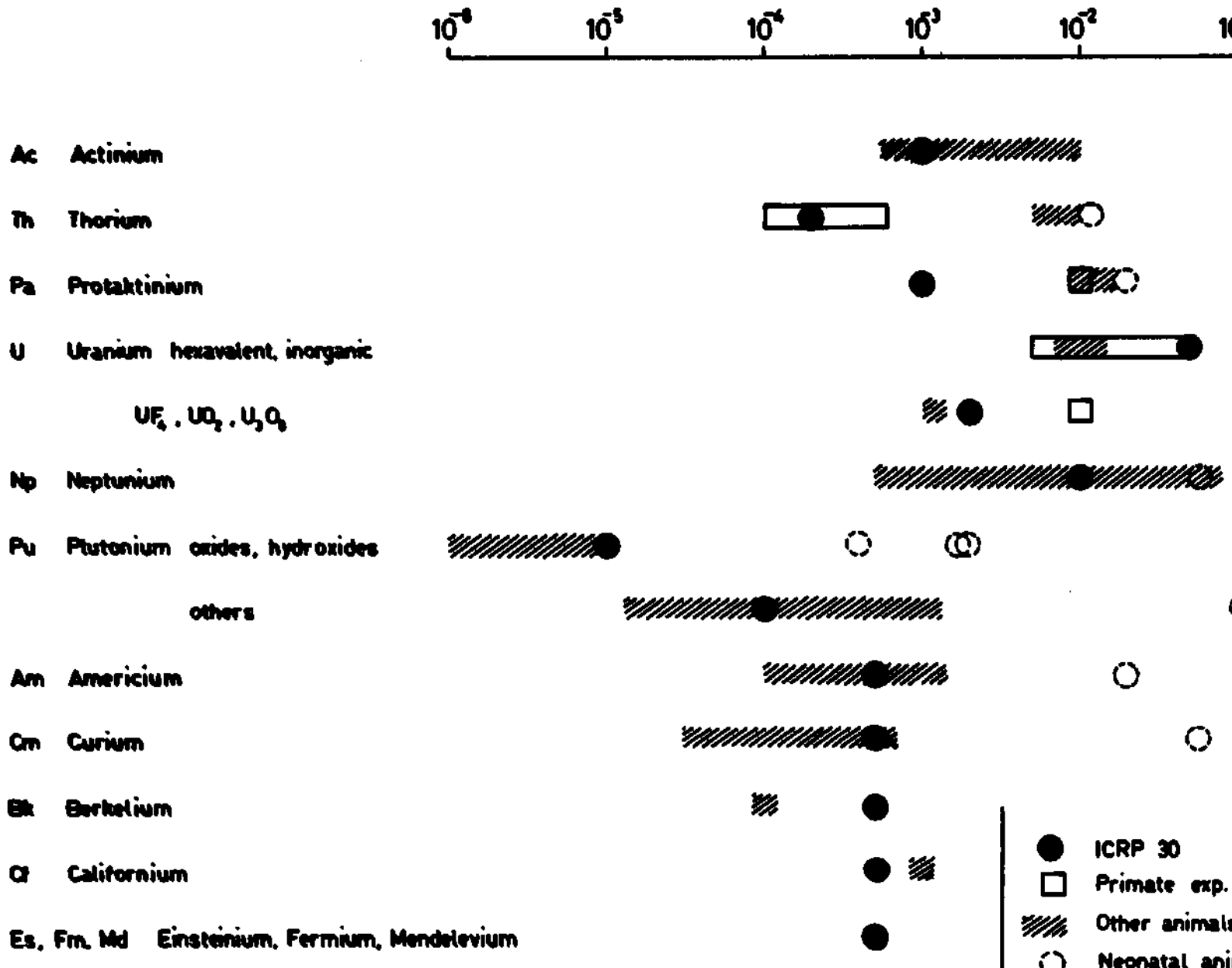
Organism	chemical form	fractional absorption	Ref.
Actinium			
rat	AcCl3	<<0.01	Ca56
man (ICRP)	all forms	0.001	ICRP78
Protactinium			
rat	Pa-231 citrate	0.01 - 0.02	Za69
hamster	Pa-231 fluoride	0.002	Ha81
rat	Pa-233 nitrate	3 x 10-4	Su83a
rat, neonatal	Pa-233 nitrate	0.026	Su83a

Organism	chemical form	fractional absorption	Ref.
(Protactinium continued)			
baboon	Pa citrate	0.01	Co83a
man (ICRP)	all forms	0.001	ICRP78
Berkelium			
rat	BkCl3	10-4	Hu72
man (ICRP)	all forms	5 x 10-4	ICRP78
Californium			
rat	Cf(NO3)3	0.001	ICRP78
man (ICRP)	all forms	5 x 10-4	ICRP78
Einsteinium			
rat	"behaves like americium"		Hu72
man (ICRP)	all forms	5 x 10-4	ICRP78
Fermium, Mendelevium			
no experimental data available			
man (ICRP)	all forms	5 x 10-4	ICRP78

III. 7 Intercomparison of GI-Uptake of Actinides

Although all actinides show low GI transfer factors, differences between the elements are quite large. In Fig. 4, the range of findings for the different animal and human systems studied are displayed. The uptake value for fired plutonium oxide in adult animals is 5 orders of magnitudes lower than the transfer factor for monomeric forms in neonatals. Generally speaking, gastrointestinal uptake as compared to other ions i.e. heavy metals, is low. The larger values found by Sullivan (Su80, Su82, Su83a) for newly born animals can be explained by the leaky intestine of neonatals which is permeable to makromolecules, e.g. food proteins (Bu87). Since factors in mother's milk induce the sealing of the infant's intestinal epithelium during the first few days after birth, even GI transfer factors temporarily higher by a factor of 100 would only produce insignificant body burdens from environmental levels of actinides in milk or water used for milk formulas.

Figure 4: Range of actinide GI transfer factors found in experiments with primates or other animals and the values adopted by ICRP, respectively (For details see the sections on specific elements).


10^{-6}
10^{-5}
10^{-4}
10^{-3}
10^{-2}
Ac Actinium
Th Thorium
Pa Protaktinium
U Uranium hexavalent, inorganic
UF_4 . UO_2 . U_3O_8
Np Neptunium
Pu Plutonium oxides, hydroxides
others
Am Americium
Cm Curium
Bk Berkelium
Cf Californium
Es, Fm, Md Einsteinium, Fermium, Mendelevium
ICRP 30
Primate exp.
Other animals
Neonatal ani

IV DISCUSSION

The available data base for gastrointestinal absorption of any of the actinides gives a fractional transfer factor of 0.05 or less. Aside from uranium and the still unresolved magnitude of neptunium GI uptake, this absorption value may even be less than a fraction of a percent for most chemical forms and experimental conditions tested thus far. This assessment clearly indicated that the gastrointestinal exposure pathway in the occupational environment was probably of minor importance. Therefore, experimental work on actinide incorporation was largely concentrated on inhalation and wound contamination.

With nuclear power coming of age, exposure to toxic transuranium elements from fission reactors became a major concern to the public. High level radioactive waste repositories will contain large amounts of plutonium, neptunium and americium even tens of thousands of years after decay of all of the important fission products. Possible leaching from these sites may lead to the contamination of ground water supplies in the distant future, and to the possible gastrointestinal uptake of actinides in subsequent generations. For the assessment of such environmental exposures to actinides in food or water, more information is needed on several points. The following is an incomplete list of some of the major uncertainties encountered in the attempt to quantify radiation exposure from absorption of actinides released do the environment.

- chemical form: at very low concentrations, the tendency

of the transuranium elements to polymerize will become less probable. Monomeric ions will be available for uptake. Natural complexing agents like humic and fulvic acids may increase the solubility of actinides in aqueous solution by orders of magnitudes. Such interaction will also have significant impacts on on the rate of transport in geological formations and on gastrointestinal uptake factors. The latter is seen dramatically in the unsuspectedly high GI transfer factor for environmental uranium (Hu73).

- Interaction with biomolecules in the body: mammals possess an intricate system of proteins with high affinities for binding specific ions both in the blood and in or on the surface of some cell types. These carrier proteins are crucial for transport and storage of ions functioning as coenzymes in biochemical reactions e.g. the iron-transferrin system. Enrichment in selected areas of the body is brought about by corresponding receptors on the surface of cells, i.e. transferrin membrane receptors for iron. The highly charged actinium ions plutonium and americium also display considerable affinity to transferrin (Ta81). Since the liver is the major iron storing organ, binding to transferrin may explain why a large fraction of the actinide activity entering the blood stream ends up in the liver. Further studies on the molecular basis of actinide uptake and transport mechanisms in the body are required to understand the biokinetics of these elements.

- GI-uptake patterns often seem to reflect specific experimental conditions more than species specific ion transporting capacities of the intestinal wall. Nutritional state, i.e. fed or fasted, in the former also amount and kind of food, may influence GI transfer factors for actinides in seemingly unpredictable ways. Interaction

with saliva or gastrointestinal contents was shown to determine crucial paramaters like solubility (Ta83) or oxidation state (Su83), respectively.

Only the application of modern biochemical and physiological techniques both in vivo and in vitro will result in an understanding of the events at the molecular level which determine uptake and transport of actinides in the body.

ACKNOWLEDGEMENTS

I would like to thank Dr. Norman Cohen for introducing me to the world of actinide biokinetics in primates. His unfailing interest in this research area and his longstanding experience with metabolic studies in baboons provided much appreciated guidance.

I also wish to express my gratitude to Dr. Rolf Grauer for his advice in the field of actinide chemistry.

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