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Occupational Internal Dosimetry, Past, Present and Future: The Actinide Example

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Resource for Internal Actinide Dosimetry and Bio-molecular Effects

Occupational Internal Dosimetry, Past, Present and Future: The Actinide Example

Scope of Presentation:

- Pre- and post-WWII origins of occupational internal dosimetry – "Tripartite Conferences on Radiation Protection (1949-1953)"
- ICRP Publication 2 (1959) – "Permissible Dose for Internal Radiation"
- ICRP Publication 30 (1979) – "Limits for Intakes of Radionuclides by Workers"
- ICRP Publications 61/68 (1991/1995) – "Annual Limits on Intake of Radionuclides by Workers Based on the 1990 Recommendations"
- *Break!*
- Current internal dosimetry "tools" – and their applications
- Sixty years' human experience of internally deposited actinides – the resources provided by the U S Transuranium & Uranium Registries

Origins of Early Radiation Protection Standards for Radionuclides Entering the Body

- The historical material that I will quote here is extracted from Dr Lauriston S Taylor's 1984 compilation of documents considered by the 1949-1953 Tripartite Conferences on Radiation Protection: Canada, United Kingdom, United States
- For rigorous study (recommended), Dr Taylor's complete compilation is published by the U S Department of Energy's Office of Scientific and Technical Information
- It is available for web download from - http://www.pnl.gov/bayesian/refs/Taylor1984_Tri-Partite_Conferences_NVO-271.pdf (Courtesy of Dr Dan Strom, Pacific Northwest National Laboratory, Richland, WA)

Pre-WWII Standards

- "Until May 1941, all of the proposed numerical radiation protection standards related to *radiation sources external to the body* This was, of course because of the manner in which radiation was used in diagnostic and therapeutic radiology
- The only deviation occurred when radium or radon, in sealed tubes or containers, was inserted into the body to increase the exposure of the tumor under treatment
- Since no radioactive material or radon gas was allowed to enter the body systems and tissue this, for all practical purposes, could be treated as an external source"

WWII Standards

- "The first recommendation for dealing with the problems of radioactive material entering the body and the body systems were made by the U.S. Advisory Committee [on X-ray and Radium Protection (later the National Committee on Radiation Protection, or NCRP)], which undertook a study in 1940 on the *safe handling* of radioactive luminous compounds.
- This activity followed recognition of the very serious injuries that were being incurred by the *radium dial painters*, a problem about which increasing concern had developed over the preceding decade."

WWII Standards (Contd.)

- "The [1941 U S Advisory] committee made two critical recommendations:
  - an upper limit for the amount of radium that might be contained within the body (body burden) without producing *unacceptable injury* In fact, the proposed level of 0 1 microgram of radium as a permissible body burden has not *since that time* been demonstrated to produce any ill effect on the recipient
  - limit the radon content in the air of workplaces; it was recommended that the concentration not be allowed to exceed 10^{-11} curies per liter [10 pCi l^{-1}] at any place, at any time
- … the Manhattan Engineer District operations to develop the atomic bomb were organized in 1942 and everything connected with radiation became highly secret until after the war
- … from the outset, the atomic energy program adopted both the external protection standards established in 1934 and the *radium protection standards recommended in 1941*"

Immediate Post-WWII Standards

- "During the war years, there had been heavy research programs on the biological effects of radiation on animals. While this was probably concentrated more in the United States, there had been important work [also] going forward in both Canada and England.
- The U.S. Advisory Committee was re-established and reorganized in 1946 as the National Committee on Radiation Protection [NCRP].
- The Atomic Energy Company, Ltd. (AECL), in Canada and the British Medical Research Council expanded their own organizations and carried out very valuable and active programs. *They were less restricted than the United States with regard to issuing reports*."

1949 – 1953: The Tripartite (Canada, UK, US) Conferences on Radiation Protection

- "The initial conference held in Chalk River, Ontario [AECL], quickly reached agreement on the new permissible dose structure originally proposed by the NCRP and subsequently by the British Medical Research Council.
  - It also accepted the concept of a permissible body burden and the value of 0 1 microgram of radium proposed by the U S Advisory Committee in 1941
  - Agreements on standards for the *great host of new radionuclides* were far more difficult to achieve, less because of basic disagreements than because of the *newness and complexity of the problems of internal emitters*
  - Tentative agreements were nonetheless reached on most of them "

1950: Reconstitution of the International Commission on Radiological Protection (ICRP)

- " … following the [1949 Tripartite] Conference, the laboratories of the three governments had to examine the recommendations in detail to insure their basic soundness and *to assess impact upon operations, especially military*
- In July 1950, less than a year after the Chalk River Conference, the ICRP was reorganized in London and set up a subcommittee structure very similar to that of the NCRP
  - A special session of the Tripartite Conference was organized by the British Atomic Energy Research Establishment [AERE, Harwell]
  - The attendees, acting in concert with the ICRP reached tentative agreement on *maximum permissible body burdens* for a dozen radioactive isotopes
  - These were published as a supplement to the 1950 [first] ICRP report "

Reconstitution of the ICRP (Contd.)

- " It was an unusual but useful step in combining the interests of these governments with an international non-governmental organization Since that time, a close but strictly unofficial collaboration had continued between them as well as other governments added later
- Nearly three years of study and research on the overall problems of standards for internal emitters of ionizing radiation followed the 1950 meeting
- The basic standards philosophy, orientated toward radiation from external sources, was sharpened and critically tested in practical operations
- The number of radionuclides for which permissible doses could be prescribed substantially increased, and it appeared desirable to make a final examination of the situation in relation to *both national defense and non-military applications* "

Tripartite and ICRP Collaboration (through 1953)

- " It was under these circumstances that the third and last Tripartite Conference was held [in Harriman, N Y] in March 1953
- All studies of the past four years were critically reviewed
- No major changes were made, but the conference achieved a much firmer sense of agreement and understanding about the overall problem of protecting people against harm from ionizing radiation
- By then, better understanding of the radiation protection problem precluded expectations of absolute safety against harm to man
- At the same time, assurances developed that radiation exposure of man could be kept within *acceptable bounds, comparable with or superior to the many other risks that we all live with*

Extract from US Minutes of Chalk River "Permissible Doses" Conference, September 1949

Radioisotope	Known or Estimated Minimal Damaging Dose	Best Estimate of Safe Dose in Body (Plant Personnel)
Radium-226	1 µg	0.1 µg
Uranium (natural)	-	-
Uranium-233	6 µg	0.6 µg
Plutonium-239	5 µg	0.5 µg
Polonium-210	-	-
Thorium-234	6-8 µCi	0.6-0.8 µCi
Strontium-90/Yttrium-90	10 µCi	1.0 µCi
Strontium-89	20 µCi	2.0 µCi

"Permissible Levels" – Recommendations of the American-British-Canadian Committee, September 1949

Substance	Body Content (μg)	Urine (μg per 24 h)	Air (μg per m³)	Water (μg per liter)
Ra	0.1	-	2×10^{-6}	4×10^{-5}
Pu	0.1	1×10^{-5}	2×10^{-6}	4×10^{-3}
Po	(1.1×10^{-6})	(1.2×10^{-9})	(3.5×10^{-9})	-
Tu	(8700)	(4.2)	25	-
2% ^{234}U Sol. Insol.	(43)	(0.02)	(0.43)	(142)
^{233}U Sol. Insol.	0.6	(3×10^{-4})	6×10^{-3} 2.5×10^{-5}	2
T (Mesothorium - ^{228}Ra)	0.1	(4.5×10^{-3})	1×10^{-4}	1×10^{-3}

"Maximum Permissible Amounts of Radioactive Isotopes" – April 1951 Supplement to ICRP Publication 1

	Ra-226	Pu-239	Sr-89	Sr/Y-90	Po-210	H-3	C-14 (CO_2)	Na-24	P-32	Co-60	I-131*
MPL in body (μCi)	0.1	0.04	2.0	1.0	0.005	10^{-4}	-	15	10	1	0.18
Effective mean life (d)	10^4	10^4	-	5000	-	10	-	0.8	20	20	12
Permissible daily deposition (μCi)	10^{-5}	4×10^{-6}	-	2×10^{-6}	-	10^{-3}	-	20	0.5	0.05	1.5×10^{-2}
Fraction absorbed from lungs	0.06	0.1	-	0.06	-	1	-	-	-	-	0.2
Fraction absorbed from intestine	0.1	10^{-3}	-	0.1	-	1	-	1	1	1	0.2

* For I-131, values shown refer to thyroid

"Present and Proposed Operating Tolerances for Los Alamos – c.f. Chalk River Proposals" (Langham 1950 Memo)

Material		Maximum Permissible Body Content (Plant Personnel)		
		LA Present	LA Proposed	CR Proposed
Ra		0.1 μg (0.1 μCi)	0.1 μg (0.1 μCi)	0.1 μg (0.1 μCi)
Pu	Soluble & Insoluble	1 μg (0.063 μCi)	0.5 μg (0.032 μCi)	0.1 μg (0.0063 μCi)
U-nat	Soluble Salts Insoluble Salts	- 15,000 μg	120 μg ? 15,000 μg	12 μg 15,000 μg
^{233}U	Soluble Salts Insoluble Salts	-	3.7 μg (0.032 μCi) 1.1 μg (0.011 μCi)	0.6 μg (0.0063 μCi) 0.2 μg (0.002 μCi)
^{235}U + 2% ^{234}U	Soluble Salts Insoluble Salts	-	240 μg 85 μg	48 μg 17 μg
Po	Soluble Salts	0.2 μCi	0.01 μCi ?	0.005 μCi

Summary: 1941 – 1953 Concepts for Occupational Radiation Protection from Internally Deposited Radionuclides

- Extension of "tolerance dose" concept for whole body radiation to radionuclides retained in body organs
  - The tolerance dose was considered to be that level of radiation to which an individual could be continuously exposed without any demonstrable ill health effect or harm
- Direct experience of "tolerance dose" for ingestion of radium (1 μCi deposited in the skeleton of female dial painters) provided the basis for deriving "maximum permissible body burdens (MPBBs)" for control of exposure of workers to plutonium during the World War II Manhattan Project
  - Also applied for other important "bone-seeking" radionuclides
- For other important radionuclides, the "tolerance dose" concept was applied for "critical" organs in which these radionuclide concentrate
  - E g , the thyroid gland for ^{131}I
- These concepts carried through to ICRP's 1959 Report of Committee II on "Permissible Dose for Internal Radiation" (ICRP Publication 2)

Example: Derivation of MPBB for Plutonium-239

- Derived from comparative toxicology studies (injected ^{239}Pu *c.f.* injected ^{226}Ra in rodents) performed at the Manhattan Project's "Metallurgical Laboratory" and the University of Rochester, NY:-

$$(MPBB)_{Pu} = 0\ 1\ \mu Ci\ Ra \left[\frac{1}{15} \times \frac{0\ 75}{0\ 25} \times \frac{4\ 8 + 0\ 5(5\ 5 + 6\ 0 + 7\ 7)}{4\ 8 + 0\ 15(5\ 5 + 6\ 0 + 7\ 7)} \right]$$

$$= 0\ 04\ \mu Ci$$

- Where:

  1/15 = ratio of toxicity ratio of radium : plutonium in rodent;
  0 75/0 25 = ratio of retention of plutonium : radon in rodent;
  0 5/0 15 = ratio of radon retention in man : rodent;
  other values are energies of α particles emitted by radon and its progeny

Application of the "MPBB" Concept – ICRP Publication 2 (1959)

- To calculate dose to individual body organ, radionuclide activity assumed to be uniformly distributed through that organ
- For γ-emitters, organs assumed to be spherical
- Simple rate constants (exponential clearance) assumed to calculate retention and number of disintegrations in body organ
- Values of "permissible" doses accumulated over specified time periods recommended for several "critical" body organs, e g , D = 5 × (N-18) rem for blood forming organs, gonads, and lens of the eye
- Values of "maximum permissible concentration" in air (MPC_a) and water (MPC_w) recommended for important radionuclides – corresponding to accumulation of specified "permissible" dose in most highly irradiated organ
- "Maximum permissible body burden" (MPBB) recommended for each radionuclide – corresponding to accumulation of "maximum permissible organ dose "

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Lung "Model" Assumed in ICRP2 (1959) to Calculate MPC_a

- Retention of particulate matter in the lungs was known to depend on many factors, such as the size, shape and density of particles, the chemical form and whether or not the person is a mouth breather
- However, when [individual-specific] data are lacking [e g , for standard setting], the distribution of particle deposition and uptake shown below was assumed

Distribution	Readily soluble compounds (%)	Other compounds (%)
Exhaled	25	25
Deposited in upper respiratory passages - subsequently swallowed	50	50
Deposited in lungs (lower respiratory passages)	25 (this is taken up into the body)	25*

*Half is eliminated from lungs and swallowed in first 24 h Remaining 12½% is retained with a half-life of 120 d (taken up into body fluids)

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Empirical Model for Pu Excretion in Urine – Human Injection Study (1949 – 1953)

In 1949, Wright Langham (Los Alamos) injected a group of "terminally ill" patients with soluble $Pu(NO_3)_4$ – and followed their urinary excretion over the next 4 y.

In 1976, John Rundo (Argonne Laboratory) found two of these original patients (HP-3 & HP-6). Their Pu excretion was still measureable!

Figure adapted from Jones, S.R. Derivation and validation of a urinary excretion function for plutonium applicable over tens of years post intake. *Radiat. Prot. Dosim.* **11**: 19-27 (1985).

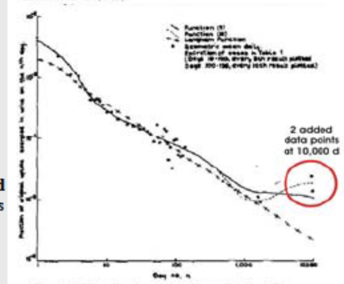

Figure 1. Time development of excretion functions.

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Developments in the 1960s and 1970s – Leading to Quantitative "Risk-Based" Radiation Protection Standards (ICRP30, 1979)

- 20 y of (worldwide) experimental studies in laboratory animals (primarily rodents) of the biokinetics and microscopic tissue distribution of all practically important radioelements -
  - especially fission products, uranium, thorium, plutonium and the trans-plutonium elements (higher actinides)
- Lifespan studies of the toxicity (carcinogenesis) of fission products, radium, radon progeny, thorium, plutonium and higher actinides in large laboratory animals (beagle dogs, baboons) -
  - Lifespan of "low-level" animals extended through the 1980s!
- The U S Transuranium Registry -
  - suggested at a Hanford Biology symposium in 1967 by H D Bruner [US Atomic Energy Commission (AEC) Headquarters];
  - set up in 1968 by W D "Dag" Norwood, the industrial physician at Hanford – under AEC contract with the Hanford Environmental Health Foundation (HEHF);
    - to track the medical history, health physics data, and tissue burdens (at autopsy) of 330 known AEC-wide transuranium element intake "cases."
    - to include cases from all major AEC sites.

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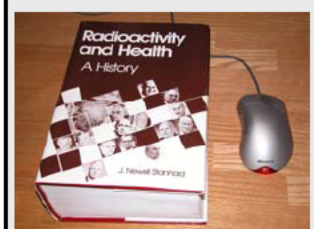
Historical Compendium of Studies on "Radioactivity and Health"



Stannard, J. N. "Radioactivity and Health: A History". Springfield, VA: National Technical Information Service (1988).

"Dr J Newell Stannard's *Radioactivity and Health: A History* is a fascinating story of scientific research and of people who provided leadership and made important discoveries It is a story of how science successfully dealt with the potential hazards of working with highly radioactive material; undertook research to understand its behavior and effects in biological and environmental media; applied this knowledge to the technology for handling radioisotopes safely and to the establishment of radiation protection standards, which have guided the design of laboratories, hospitals, and factories where radioisotopes are produced and used "

William J. Bair Battelle Pacific Northwest Laboratories Richland WA (in his Foreword to Professor Stannard s 1988 book).

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Radium Dial Painters, Ottawa, Illinois (ca. 1924)

Dial painters at their desks Note open trays of luminized dials – tightly packed workers!

Photo courtesy of Drs Finkel & Miller (Argonne Radium Study) – used to trace workers

From Stannard, J. N. "Radioactivity and Health: A History". Springfield, VA: National Technical Information Service (1988).

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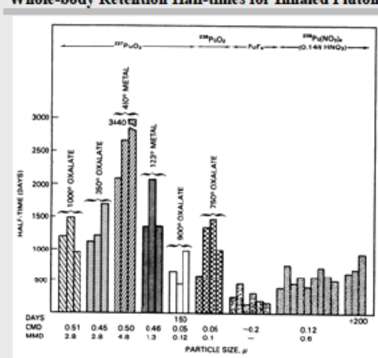
Whole-body Retention Half-times for Inhaled Plutonium in Dogs (Bair, 1970)



From Stannard, J. N. "Radioactivity and Health: A History". Springfield, VA: National Technical Information Service (1988).

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Effects of Cigarette Smoking on Lung Clearance and Toxicity – Smoking Beagles! (Filipy et al., 1980)

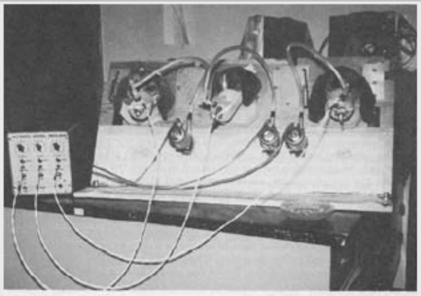

FIGURE 9.21. Mask assembly for the smoking beagles. (Photo courtesy of Pacific Northwest Laboratory.)

From Stannard, J. N. "Radioactivity and Health: A History". Springfield, VA: National Technical Information Service (1988).

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Presenter's Personal Perspective: From 1960's Experimental Microdosimetry of Pu in Skeleton of Laboratory Rat to Pu in Human Tissues up to 60-y Post Intake!

MRC/NRPB, UK (1970-1988)

Battelle PNL, Richland, WA (1988-1994)

(1995-2004)

USTUR/WSU Richland/Pullman, WA (2004 - 2010)

Royal Free Hospital School of Medicine, London, UK (1965-69)

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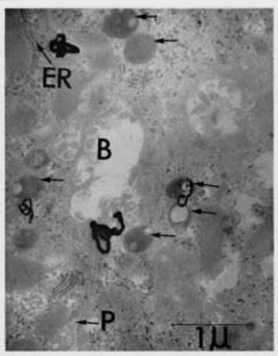
Electron Microscope Autoradiography of ^{241}Pu – Sub-cellular Localization in Rat Liver Parenchymal Cell (James and Rowden, 1969)



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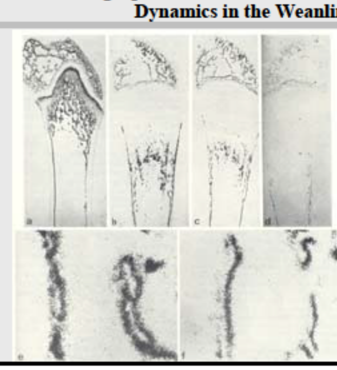
Autoradiographic Visualization of Bone Growth/Chelation Dynamics in the Weanling Rat



From James and Taylor, 1971

Key

i v injection of citrate-buffered (monomeric) $^{239}Pu(NO_3)_4$ – 5 μCi/kg

- a 1 d untreated
- b 21 d untreated
- c DTPA at 7 d
- d DTPA at 30 min
- e From [b] - untreated
- f From [c] – DTPA 7 d

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Deposition of Radon Progeny in the Bronchial Tree – Ventilated Excised Pig Lung (James, 1977)

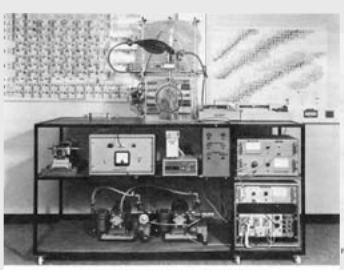

FIG. 3. Apparatus used to ventilate excised pig lung.

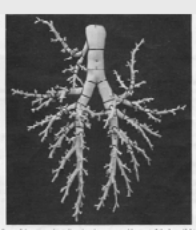

FIG. 6. Some of the units made at dissection shown on a rubber cast of the bronchial tree (pig).

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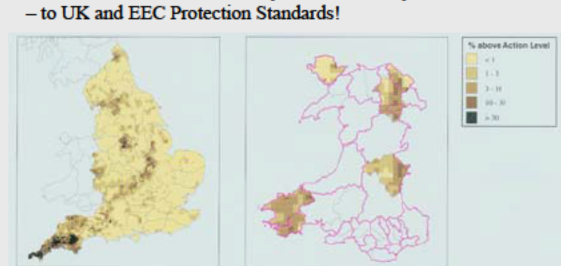
Radon Progeny Research at NRPB (1972 – 88)

- From metrology and monitoring (instrumentation) - through biokinetics, bronchial dosimetry, national survey of radon in homes – to UK and EEC Protection Standards!



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Rodent Studies of Inhaled Industrial Actinide Dusts (1974-on)

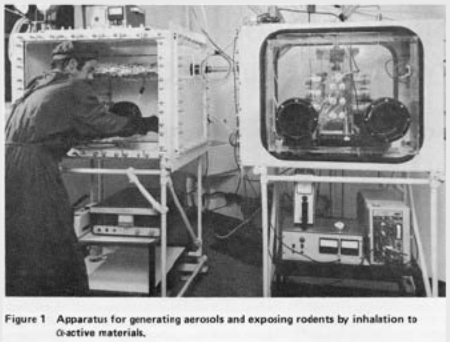

Figure 1 Apparatus for generating aerosols and exposing rodents by inhalation to α-active materials.

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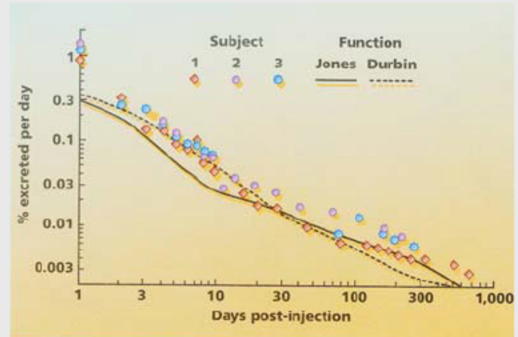
Current UK Human Studies of Inhaled and Injected Pu Isotopes



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The U.S. Transuranium and Uranium Registries

- Originated in 1968 as "U S Transuranium Registry" (USTR) - at Hanford Environmental Health Foundation (HEHF)
- For a detailed history of the development of USTR, it's sister "U S Uranium Registry," the associated radiochemical analysis laboratories – and their consolidation (as USTUR) in 1992 at WSU's College of Pharmacy (Richland Campus) and the Nuclear Reactor Center (Pullman) – see http://www ustur wsu edu/history html
- Ron Kathren, CHP (the first non-physician!) led the consolidation of USTUR at WSU – and directed USTUR's work from 1992 – 1998
- Ron Filipy, Ph D , followed as USTUR Director (1999 – 2005)
- We are now (from July 1st) embarking on a new 5-y USDOE grant renewal and research program!

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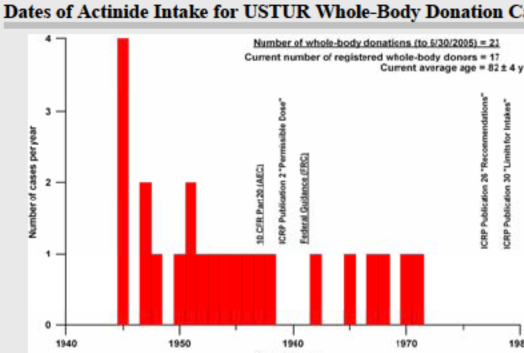
Dates of Actinide Intake for USTUR Whole-Body Donation Cases



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More Later of Current Research into Actinide Biokinetics - Followed "Long-term" in Actual Workers!

- Almost all of USTUR's Registrants received their "intakes" under the (pre-1980s) "permissible dose" and "body burden" regulatory control system.
- I now want to run (briefly) through the changes in regulatory control of occupational internal exposures (in the U.S. and internationally) that have occurred since then!
- ***How well did the early regulatory control system do? – by today's standards!***

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"Risk-Based" Radiation Protection Standards – ICRP Publication 26 (1977)

- ICRP Publication 26 (1977) - "Recommendations of the International Commission on Radiological Protection".
- Established dose limitation system designed to:
  - prevent "non-stochastic" effects;
  - limit "stochastic" effects;
  - introduce quantitative concept of "risk".

Prevention of Non-stochastic (Threshold) Effects

- Non-stochastic dose limits based on 50-year organ doses:

$$D_T = \frac{E_{abs,T}}{M_T} \quad [\text{in gray}\,(Gy),\text{or rad}] \;\ldots\ldots\ldots (1)$$

$$H_T = \sum_R w_R\, D_{T,R} \quad [\text{in sievert}\,(Sv),\text{or rem}] \quad \ldots\ldots\ldots (2)$$

Limitation of Stochastic (Probabilistic) Effects

- Stochastic dose limits set by considering ***total*** effects of organ doses (including external dose) on ***whole body***:

$$E = \sum_T w_T\, H_T \quad [\text{in sievert}\,(Sv),\text{or rem}] \quad \ldots\ldots\ldots (3)$$

where; E is the *Effective Dose (committed over 50-y)*;
w_T is the *Tissue Weighting Factor*;
and H_T is the *Committed Equivalent Dose*

Application of ICRP26 Recommendations to Internal Dosimetry – ICRP Publication 30 (1979)

"Limits for Intakes of Radionuclides by Workers"

- **Reference Worker** - adult male
- **Dose coefficient** - *committed* (*50-y*) equivalent dose in organ T resulting from intake I:

$$H_T(\tau) = \int_{t_0}^{t_0+\tau} H'_T(t)\,dt \quad \ldots\ldots\ldots (4)$$

$$H_T(\tau) = I\, h_T(\tau) \quad \ldots\ldots\ldots (5)$$

$$h_T = \sum_S \sum_j U_{S,j}\, SEE(T \leftarrow S)_j \quad \ldots\ldots\ldots (6)$$

$$SEE(T \leftarrow S) = \sum_R \frac{E_R\, Y_R\, w_R\, AF(T \leftarrow S)_R}{m_T} \quad \ldots\ldots\ldots (7)$$

ICRP Publication 30 (1979) – Operational Quantities

"Limits for Intakes of Radionuclides by Workers"

- ***Annual Limit on Intake*** (*ALI*) defined as largest value of I which satisfies:

$$I \sum_T w_T\, H_{50,T} \le 0.05\ Sv \quad \ldots\ldots\ldots (8) \quad \textit{for stochastic effects}$$

$$I\, H_{50,T} \le 0.5\ Sv \quad \ldots\ldots\ldots (9) \quad \textit{for nonstochastic effects}$$

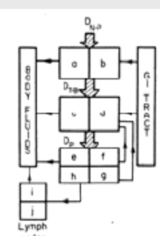
ICRP30 (1979) – Tissue Weighting Factors, w_T

Organ or tissue	w_T
Gonads	0.25
Breast	0.15
➡ Red bone marrow	0.12
Lung	0.12
Thyroid	0.03
➡ Bone surfaces	0.03
➡ Remainder	0.30

ICRP30 (1979) – Practical Implementation of ICRP26

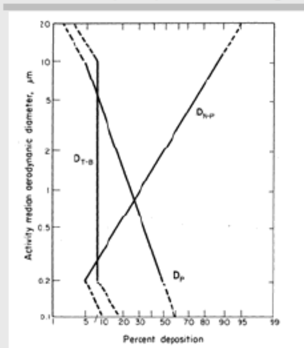
- **Adopted the 1966 "Lung Model" developed by the "Task Group on Lung Dynamics" (TGLD).**

Region	Compartment	Class D T day	Class D F	Class W T day	Class W F	Class Y T day	Class Y F
N–P (D_{N-P} = 0.30)	a	0.01	0.5	0.01	0.1	0.01	0.01
	b	0.01	0.5	0.40	0.9	0.40	0.99
T–B (D_{T-B} = 0.08)	c	0.01	0.95	0.01	0.5	0.01	0.01
	d	0.2	0.05	0.2	0.5	0.2	0.99
P (D_P = 0.25)	e	0.5	0.8	50	0.15	500	0.05
	f	n.a.	n.a.	1.0	0.4	1.0	0.4
	g	n.a.	n.a.	50	0.4	500	0.4
	h	0.5	0.2	50	0.05	500	0.15
L	i	0.5	1.0	50	1.0	1 000	0.9
	j	n.a.	n.a.	n.a.	n.a.	∞	0.1



Resource for Internal Actinide Dosimetry & Bio-molecular Effects — Slide 43

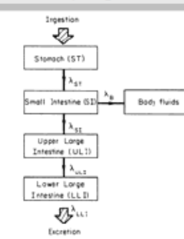
ICRP30 (1979) – Particle Deposition Model (TGLD, 1966)



- Regional lung deposition defined by the *Activity Median Aerodynamic Diameter* (*AMAD*) of the inhaled aerosol particles
- Default AMAD = 1 µm
- Corresponding (default) regional deposition:
  - D_{N-P} = 30%;
  - D_{T-B} = 8%;
  - D_P = 25%

Resource for Internal Actinide Dosimetry & Bio-molecular Effects — Slide 44

ICRP30 (1979) – Gut Model (adapted from Dolphin & Eve, 1966)



Section of GI tract	Mass of walls* (g)	Mass of contents* (g)	Mean residence time (day)	λ day⁻¹
Stomach (ST)	150	250	1/24	24
Small Intestine (SI)	640	400	4/24	6
Upper Large Intestine (ULI)	210	220	13/24	1.8
Lower Large Intestine (LLI)	160	135	24/24	1

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ICRP30 (1979) – Metabolic Model for Organs of Translocation

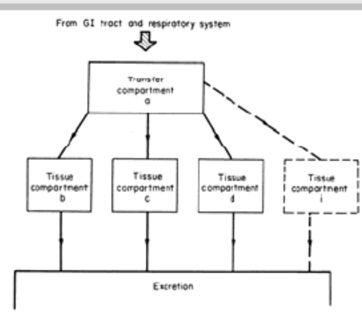

Fig. 4.1. Mathematical model usually used to describe the kinetics of radionuclides in the body: exceptions to this model are noted in the metabolic data for individual elements

Resource for Internal Actinide Dosimetry & Bio-molecular Effects — Slide 46

ICRP30 (1979) – Values of Organ Mass (ICRP23, 1975 – "Report on Reference Man")

Table 4.1. Masses of organs and tissues of Reference Man used in this Report

Source organs	Mass (g)	Target organs	Mass (g)
Ovaries	11	Ovaries	11
Testes	35	Testes	35
Muscle	28 000	Muscle	28 000
Red marrow	1 500	Red marrow	1 500
Lungs	1 000	Lungs	1 000
Thyroid	20	Thyroid	20
ST content	250	Bone surface	120
SI content	400	ST wall	150
ULI content	220	SI wall	640
LLI content	135	ULI wall	210
Kidneys	310	LLI wall	160
Liver	1 800	Kidneys	310
Pancreas	100	Liver	1 800
Cortical bone	4 000	Pancreas	100
Trabecular bone	1 000	Skin	2 600
Skin	2 600	Spleen	180
Spleen	180	Thymus	20
Adrenals	14	Uterus	80
Bladder content	200	Adrenals	14
Total body	70 000	Bladder wall	45

Resource for Internal Actinide Dosimetry & Bio-molecular Effects — Slide 47

ICRP30 (1979) –Treatment of Bone-Seeking Radionuclides

- All radionuclides classified as either *Surface-seeker* or *Volume-seeker*:
  - Surface seekers;
    - all isotopes of Th, Pu, Am, Cm, higher actinides
    - all isotopes of other elements with radioactive half-life < 10 d
  - Volume seekers;
    - Ra, U, other radionuclides distributed uniformly in body organs
- For α- and β-emitters (short-range particulate radiation), the fraction of emitted energy absorbed in sensitive target tissue (bone surface osteogenic cells and red bone marrow) is *higher for bone surface seekers* than for volume seekers
  - Takes care of "toxicity ratio" plutonium : radium (observed in experimental animals)

Resource for Internal Actinide Dosimetry & Bio-molecular Effects — Slide 48

ICRP Publication 30 – Parts 1 to 4 (1979-85)

1. Introduced new *metabolic* models – for all radioelements of practical importance:
   - *Linear first-order equations* describe translocation of material (from respiratory tract and body organ "compartments")
   - Organ deposition from transfer compartment (blood) occurs *rapidly*
   - Excretion (to urine/feces) occurs *directly* from organs and tissues
2. Published comprehensive set of *ALIs* and *DACs*.
3. However, all ICRP30 models designed for *dose/risk limitation* - not for individual *dose assessment* (bioassay).

U.S. Federal Implementation of ICRP26/30

- ICRP26-recommended concepts of *Committed Effective Dose* and corresponding Secondary Operational Standards (*ALIs* and *DACs*) not formally adopted in U.S. for occupational radiation protection until 1993:
  - U S Department of Energy Occupational Radiation Protection; final rule *10 CFR Part 835* Washington DC: Federal Register 58:65460; 1993
- Special treatment of skin dose introduced in 10 CFR 835.

Practical Implementation of 10 CFR 835 for Internal Emitters

- USDOE Office of Worker Protection Policy and Programs (EH-52) funded the Pacific Northwest National Laboratory (PNNL) to develop the software code *CINDY* (Code for Internal Dosimetry) to enable all DOE sites (and USNRC-regulated sites) to carry out bioassay and internal dose assessments in compliance with 10 CFR 835
  - U S Department of Energy Occupational Radiation Protection; final rule 10 CFR Part 835 Washington DC: Federal Register 58:65460; 1993
- Commercially licensed to individual users by Canberra Nuclear Inc , One State Street, Meridan, CT, 06450 Tel (203) 238-2351

Meanwhile – Back at ICRP!

- ICRP Publication 26 Recommendations (1977) replaced by new recommendations:
  - International Commission on Radiological Protection (ICRP) 1990 recommendations of the International Commission on Radiological Protection Oxford: Pergamon Press; *ICRP Publication 60*; Ann ICRP 21(1-3); 1991
- ICRP Publication 30 Lung Model (TGLD, 1966) replaced by new "Human Respiratory Tract Model (HRTM)":
  - International Commission on Radiological Protection (ICRP) Human respiratory tract model for radiological protection Oxford: Elsevier Science Ltd ; *ICRP Publication 66*; Ann ICRP 24(1-3); 1994

What Did ICRP Publication 60 Change?

- Revised (increased) overall radiation risk estimates.
- Added consideration of "radiation detriment."
- Revised tissue weighting factors, w_T - including more organs and "accounting" rules for "remainder tissues" and "rest of body."
- Lowered annual dose limits – from 50 mSv (5 rem) to ***20 mSv*** (***2 rem***).

ICRP's 1990s Scramble to Implement Publication 60 and Improve Dose Assessment Methodologies!

- Replaced ICRP Publication 26 (1977) Recommendations by ICRP Publication 60 (1991):
  - International Commission on Radiological Protection (ICRP) 1990 recommendations of the International Commission on Radiological Protection Oxford: Pergamon Press; *ICRP Publication 60*; Ann ICRP 21(1-3); 1991
- Replaced ICRP Publication 30 Lung Model (TGLD, 1966) by new "Human Respiratory Tract Model (HRTM)":
  - International Commission on Radiological Protection (ICRP) Human respiratory tract model for radiological protection Oxford: Elsevier Science Ltd ; *ICRP Publication 66*; Ann ICRP 24(1-3); 1994

ICRP's 1990s Scramble (Continued)!

- More realistic "*biokinetic*" models:
  - ICRP Publication 67 (1963) – including *transuranics*
  - ICRP Publication 69 (1995) – including *uranium*
- Revised dose coefficients (dose per unit intake) and secondary standards (ALIs) following implementation of new HRTM and biokinetic models:
  - ICRP Publication 68 (1994) – *Workers* (Inhalation and Ingestion)
  - ICRP Publication 69 (1995) – *Members of the Public* (Age-dependent doses from *Ingestion*)
  - ICRP Publication 71 (1995) – *Members of the Public* (Age-dependent doses from *Inhalation*)
  - ICRP Publication 78 (1997) – *Workers* [*Bioassay Functions* (*IRFs*) to replace those in Publication 54 (1988)]

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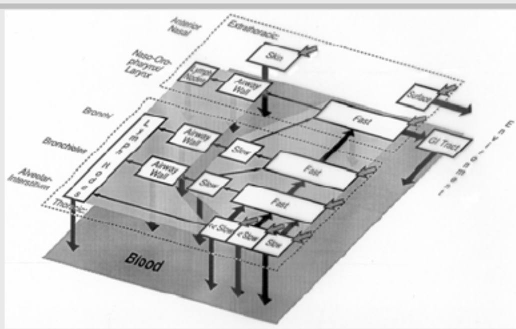
Key Feature of HRTM (ICRP 66) – Competitive Clearance Mechanisms!



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Other Key Features of HRTM

- More *realistic* (mechanistic) than ICRP30 model for ***deposition***, ***clearance*** and ***dosimetry*** (target cells at risk)
- Designed for both ***dose limitation*** and ***dose assessment***
- Age-dependent – including all members of the public
- Aerosol size range 0 0006-µm-AMTD through 100-µm-AMAD – including large particle "inhalability" – also treats gases and vapors
- ICRP30 "solubility classifications" (D, W and Y) replaced by default "*absorption types*" (***F***, ***M*** and ***S***)
- Ability to represent absorption behavior of *specific materials*
- New dosimetry of alveolar-interstitial (AI), bronchiolar (bb), bronchial (BB), thoracic lymph nodes (LNTH), and extrathoracic tissues (ET1, ET2, and LNET)
- Extrathoracic tissues recognized as potentially "at risk "
- Lung tissue weighting factor (w_{lung} = 0 12) sub-divided into fractions: 0 333 for AI; 0 333 for bb; 0 333 for BB, and 0 001 for LNTH
- **Details given in CD-ROM handout – PPT file – "Implementing the ICRP 66 Respiratory Tract Models" – AAHP Course Lecture (HPS, 2004).**

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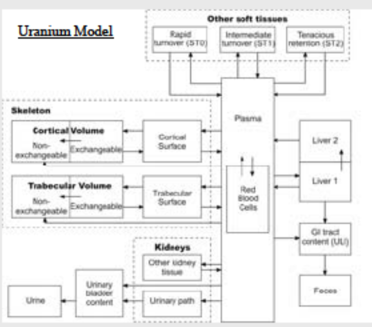
Key Features of ICRP's New "Biokinetic" Models



- ***Explicit excretion pathways.***
- ***Recycling from organs back into blood.***
- ***Organ uptake determined by competing rates.***

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That Concludes the Historical/Background "Stuff"

- ***Let's Take a Break Here!***

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USDOE Practical Response to ICRP Publication 60/68 Recommendations

- DOE Standard: Internal Dosimetry DOE-STD-1121-98 Washington, D C : U S Department of Energy; 1999 –
  - Allows use of "best science" biokinetic models in regulatory dose assessments
  - Retains *10-CFR-835* tissue weighting factors – and treatment of "Remainder Tissues"
- In July 2001, DOE's Office of Worker Protection Policy & Programs (EH-53) contracted ACJ & Associates, Inc to develop [with the UK National Radiological Protection Board (NRPB)] a new ICRP60/68-based internal dosimetry and bioassay analysis code for use by DOE-regulated sites:
  - **IMBA Expert™ USDOE-Edition**;
  - Phase II (Final) version delivered April, 2004

Resource for Internal Actinide Dosimetry & Bio-molecular Effects — Slide 60

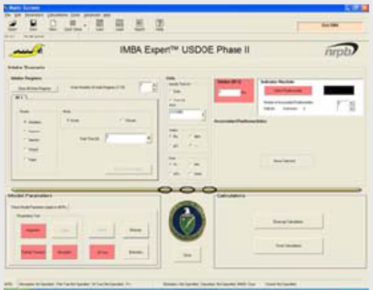
Origin of "IMBA"

- "IMBA" – Integrated Modules for Bioassay Analysis.
- 1997 – 2000: Collaborative UK development -
  - National Radiological Protection Board (NRPB);
  - British Nuclear Fuels plc (BNFL);
  - Westlakes Research Institute (WRI);
  - Atomic Energy Authority Technology (AEAT);
  - Atomic Weapons Establishment (AWE)
- *Purpose* - to develop suite of core software modules (DOS) specifically to implement all current ICRP models for estimating intakes and doses from bioassay measurements (for compliance with Euratom Directive – UK IRR 2000)

IMBA Expert™ USDOE-Edition

Aim: To provide USDOE sites with standardized methods for dealing with bioassay measurements (using QA'd IMBA modules) –

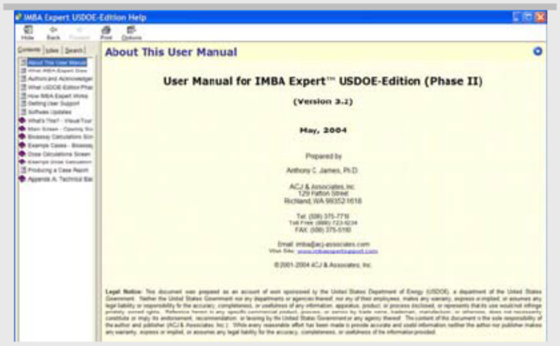
- more powerful and flexible than existing software



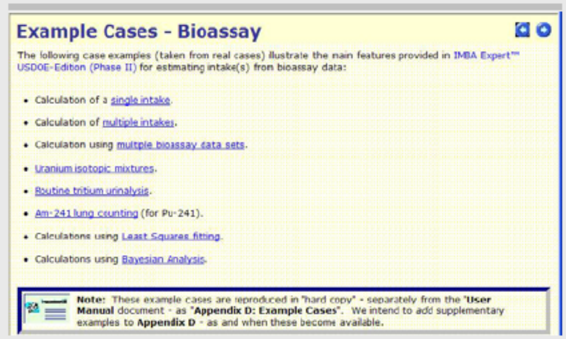
USDOE Sites Currently Licensed to Use IMBA Expert™

- Bechtel-Bettis Atomic Power Laboratory,
- Bechtel-NV, Las Vegas, NV
- BWXT PANTEX, Amarillo, TX
- BWXT Y-12, Oak Ridge, TN
- BNFL-INEL, Idaho Falls, ID
- BWX Technologies, Lynchburgh, VA
- BNFL-AMWTP, Idaho Falls, ID
- BNFL-ETTP, Oak Ridge, TN
- BNFL-INEL, Idaho Falls, ID
- Brookhaven National Laboratory (BNL), Upton, NY
- CDC/NIOSH/OCAS, Cincinnati, OH
- Lawrence Berkeley National Laboratory (LBNL), Berkeley, CA
- Lawrence Livermore National Laboratory (LLNL), Livermore, CA
- Los Alamos National Laboratory, (LANL), Los Alamos, NM
- Nuclear Fuel Servises, Inc. (NFS), Erwin, TN
- Oak Ridge National Laboratory (ORNL), Oak Ridge, TN
- Pacific Northwest National Laboratory (PNNL), Richland, WA
- Sandia National Laboratory (SNL), Albuquerque, NM
- Savanah River Site (SRS), Aiken, SC
- SEC-Jacobs, Oak Ridge, TN
- U.S. Army-AMSAM, Redstone Arsenal, AL
- U.S. Army-CHPPM, Aberdeen Proving Grounds, MD
- U.S. Department of Energy, Office of Environment & Health (EH), Germantown, MD
- Waste Isolation Pilot Plant (WIPP), Carlsbad, NM

What IMBA Expert™ Does – And How It Works!



Example Bioassay Cases (from CHM File)



Handout Material on IMBA Expert™ USDOE-Edition

- ***Your CD-ROM includes:***
  - **Interactive "Compiled HTML Help" file –** *IMBAX.CHM.*
    - **"User Manual for IMBA Expert™ USDOE-Edition (Phase II)" –** *IX2_UM_3_2.pdf.*
    - **"Appendix A: Technical Basis" –** *IX2_A_3_2.pdf.*
  - **"Appendix D: Example Bioassay Cases" –** *IX2_D_3_2.pdf .*

Other Current Versions of IMBA Expert™

- CANDU-Edition:
  - Customized for Canadian users – Partners of the CANDU Owners Group (COG) – *regulatory dose assessments*
  - Includes special models for organic tritium and carbon compounds
- OCAS-Edition:
  - Customized for use by internal dose assessors in support of the Energy Employee's Occupational Injury Compensation Program Act (EEOICPA, 2000)
  - Calculates equivalent dose received annually by specified body tissues – for input to the Interactive Radiation Epidemiology Program (IREP) – *causation probability*

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Commentary on Application of IMBA Expert™ Methodology

- Designed to apply statistical methods (maximum likelihood, least squares, Bayesian analysis):
  - For "*unbiased*" estimate of intake(s) based on available bioassay data and realistic estimates of data uncertainty
- *Regulatory Use:*
  - Subject to over-riding "Regulatory Guidance"
- *Compensation (EEOICPA) Use:*
  - Mandatory policy over-ride - intake assessments *must* favor claimant, i e , be *biased* intentionally to *overestimate* dose
- *Research Use (e.g., by USTUR – see following):*
  - Takes full advantage of built-in methods for *un-biased* intake(s) characterization
- *N.B. - Litigation Use (in hands of Expert for Defense!):*
  - *As per "Research Use" – Best Science – Un-biased.*

Resource for Internal Actinide Dosimetry & Bio-molecular Effects — Slide 68

Testing and Improving Biokinetic and Bioassay Models for the Actinides – The USTUR's Research Program

- USTUR has the responsibility to collect, organize, and make available to the global research community the data on actinide behavior in the human body gained from the gifts of its registrant donors – as expeditiously as possible
- However, in parallel with making the raw data generally available (subject to full protection of donor privacy), the Registries is carrying out quite an ambitious program of mathematical modeling research whereby the case data are:
  - *Interpreted using current bioassay analysis methodologies.*
  - *Interpreted directly in relation to currently used (or proposed) actinide biokinetic models.*

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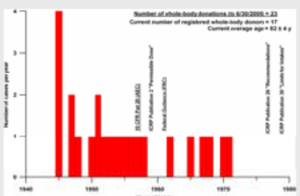
Potentially Available Data To Test Models - Over Six Decades!



•Most (and higher) exposures occurred in the 1940s and 1950s!

- Routine Autopsy (partial body) donors:
  - Number with completed radiochemical analyses = 284
  - Number with incomplete radiochemical analyses = 46
  - Number still living;
    - Category 1 = 99
    - Category 2 = 24

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USTUR Whole Body Donations Under Modeling Analysis

USTUR Case No	Work Site	Cause of Death	Primary Intake(s)	Residence Time (y)[1]
0193		Cardiovascular disease	Inhalation - acute	37
0208		Pulmonary embolus	Inhalation - acute	37
0213		Lung carcinoma	Inhalation - acute	37
0242		Cardiovascular disease	Inhalation - acute	29
0262		Hepatocellular carcinoma	Wound - single	33
0269		Prostate adenocarcinoma	Inhalation - acute	38
0425		Bronchopneumonia	Inhalation - chronic	35
0744		Cardiovascular disease	Inhalation & wound	29
0769		Osteosarcoma	Wound - single	45

[1]Residence time = time between exposure (or potential exposure) and death, calculated by the method descr bed in Fi ipy and Kathren (1996).

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USTUR's Living Registrants for Whole Body Donations

USTUR Case No.	Current Age, y	Renewal Date	Primary Radionuclide(s)	Work Site
0249		2/2008	$^{239/2}$ ^{0}Pu	
0266		12/2008	$^{239/2}$ ^{0}Pu/^{2} ^{1}Am	
0303		2/2008	$^{239/2}$ ^{0}Pu	
0391		5/2005	$^{239/2}$ ^{0}Pu/^{2} ^{1}Am	
0407		1/2009	$^{239/2}$ ^{0}Pu	
0409		7/2009	$^{239/2}$ ^{0}Pu	
0433		1/2006	$^{239/2}$ ^{0}Pu/^{2} ^{1}Am	
0631		5/2009	$^{239/2}$ ^{0}Pu	
0634		2/2008	$^{239/2}$ ^{0}Pu	
0740		1/2009	$^{239/2}$ ^{0}Pu	
0745		7/2009	$^{239/2}$ ^{0}Pu	
0757		7/2009	$^{239/2}$ ^{0}Pu	
0816		9/2005	$^{239/2}$ ^{0}Pu	
0834		8/2006	$^{239/2}$ ^{0}Pu	
0842		7/2009	^{238}Pu	
0846		1/2005	^{2} ^{1}Am	
1060		1/2009	^{23} $^{/235}$ ^{238}U	

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What Do We Mean By "Predictive Model"? – The Software Toolbox

Computational Requirements

1. Solve model in time steps – corresponding to urine/fecal sampling interval.
2. Vary ALL parameter values.
3. Evaluate "goodness-of-fit" to urine/fecal data.
4. *Fast cycle time* – for iterative "parameter seeking".
   - Birchall & James (1989) – with modern 32-bit compiler.

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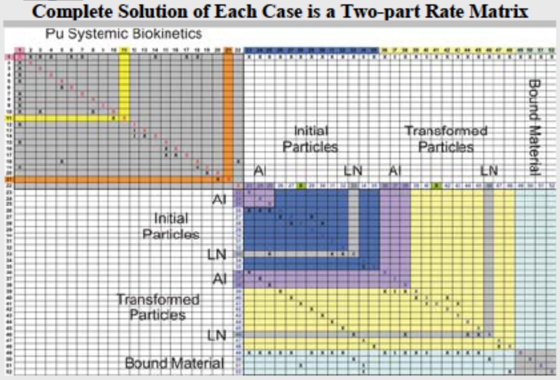
Complete Solution of Each Case is a Two-part Rate Matrix



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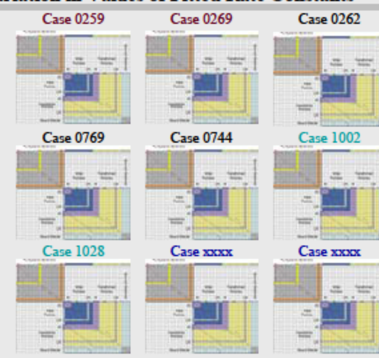
Determine Variation in Values of Fitted Rate Constants

Objective

Solve Rate Matrix for *Every* USTUR Whole-Body Case – i.e., *Define Human Population Distribution!*



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Taster Cases! – Publications Currently in Preparation

- **USTUR Case # 0262:**
  - Two acute inhalations + skin puncture wound (mid-1950s)
  - Died in 1990 (12,536 d)
- **USTUR Case # 0269:**
  - Single acute inhalation of $Pu(NO_3)_4$ (early 1950s)
  - Extensively chelated – Ca-EDTA from first day
  - Ca-DTPA after 3 years
  - Died in 1990 (14,454 d)

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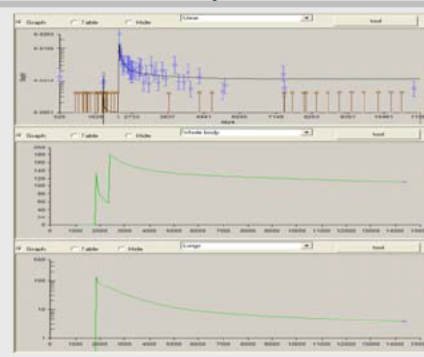
Case #0262 – First Step: Characterize Intakes



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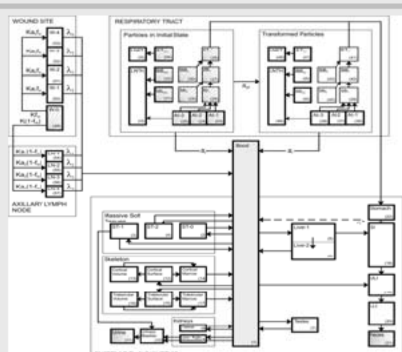
Case #0262: Combined Inhalation/Wound Model



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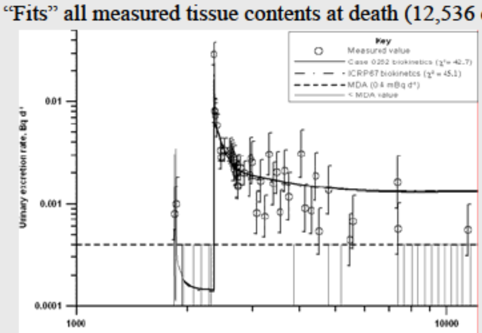
Final Model Solution for Case #0262

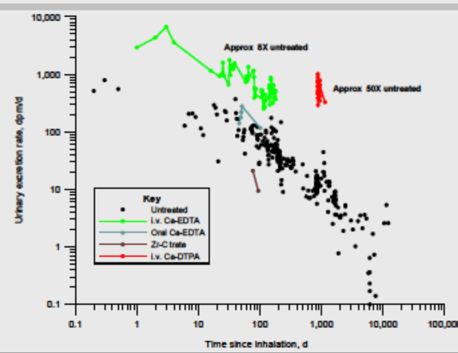
- "Fits" all measured tissue contents at death (12,536 d).



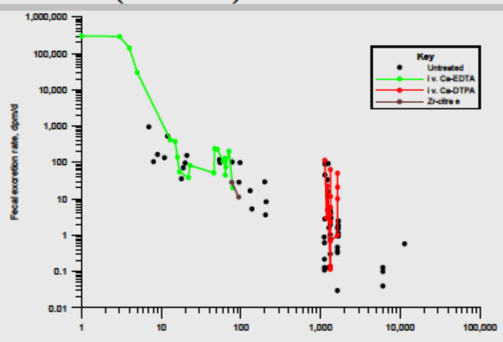
Comparison of Model Solutions for Two Cases

Transfer Pathway	Transfer Rate, d^{-1}		
	ICRP Reference Value	Case-specific Factor	
		Case #0259[a]	Case #0262[b]
Blood to Cortical bone surface	0.3235 × 0.4	× 0.515	× 0.444
Cortical bone volume to Marrow	0.0000821	× 0.55	× 0.53
Blood to Trabecular bone surface	0.3235 × 0 6	× 1.1253	× 1.133
Trabecular bone surface to Volume	0.000247	× 1.40	× 1.40[c]
Trabecular bone surface to Marrow	0.000493	× 1.00	× 1.00
Trabecular bone volume to Marrow	0.000493	× 0.64	× 0.35
Trabecular marrow to Blood	0.0076	× 0.605	× 0.605[c]
Blood to Liver 1	0.1941	× 1.61	× 0.928
Liver 2 to Blood	0.000211	× 0.92	× 0.90
Blood to Other kidney tissue	0.00323	× 1.255	× 0.827
Other kidney tissue to Blood	0.00139	× 0.97	× 1.00
Blood to Urinary path	0.00647	× 1.39	× 0.90
Blood to Urinary bladder content	0.0129	× 1.39	× 0.90
Blood to ST-2	0.0129	× 0.87	× 1.84
ST-2 to Blood	0.000019	× 1.00	× 1.00
Blood to Testes	0.00023	× 0.85	× 0.69
Testes to Blood	0.00019	× 1.00	× 1.00

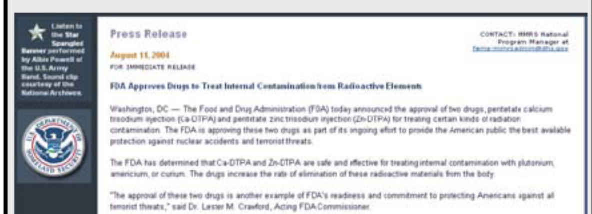
Case 0269 (Chelation) – $^{239/240}$Pu-in-Urine Data



Case 0269 (Chelation) – $^{239/240}$Pu-in-Feces Data



Why is Chelation Therapy for Internal Actinide Deposition Still of Interest?


Press Release

CONTACT: HMRS National Program Manager at

August 11, 2004

FOR IMMEDIATE RELEASE

FDA Approves Drugs to Treat Internal Contamination from Radioactive Elements

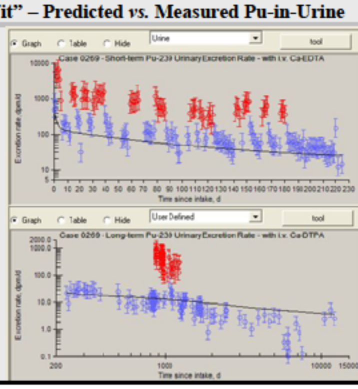
Washington, DC — The Food and Drug Administration (FDA) today announced the approval of two drugs, pentetate calcium trisodium injection (Ca-DTPA) and pentetate zinc trisodium injection (Zn-DTPA) for treating certain kinds of radiation contamination. The FDA is approving these two drugs as part of its ongoing effort to provide the American public the best available protection against nuclear accidents and terrorist threats.

The FDA has determined that Ca-DTPA and Zn-DTPA are safe and effective for treating internal contamination with plutonium, americium, or curium. The drugs increase the rate of elimination of these radioactive materials from the body.

"The approval of these two drugs is another example of FDA's readiness and commitment to protecting Americans against all terrorist threats," said Dr. Lester M. Crawford, Acting FDA Commissioner.

•*Homeland Security* – precipitates FDA approval (2004) of Ca- and Zn-DTPA – after 50-y AEC/ERDA/DOE experience of therapeutic use as "experimental" drug!

First Step: "Best Fit" – Predicted *vs.* Measured Pu-in-Urine



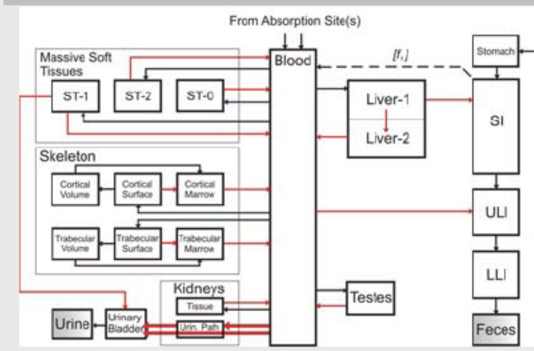
Assumes

1. No treatment
2. ICRP-Recommended parameter values in ICRP67 biokinetic model ("hard wired" in software)

General Biokinetic Model for Inhaled Plutonium

Resource for Internal Actinide Dosimetry & Bio-molecular Effects Slide 85

ICRP 67 Pu Biokinetic Model – Potential Chelation Pathways



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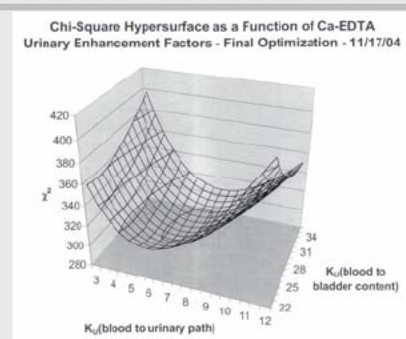
Method Used to "Fit" Parameter Values



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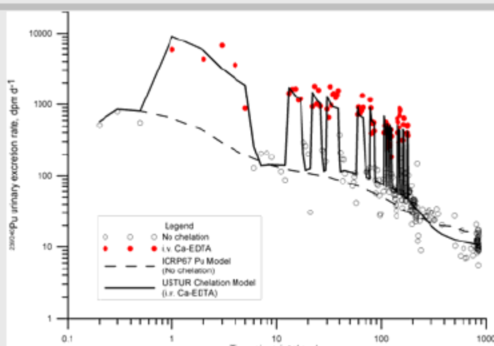
Ca-EDTA: Model of Pu-in-Urine Excretion



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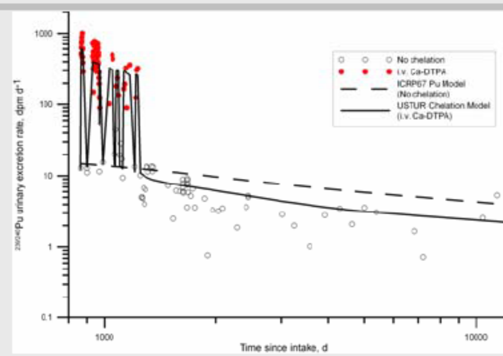
Ca-DTPA: Model of Pu-in-Urine Excretion



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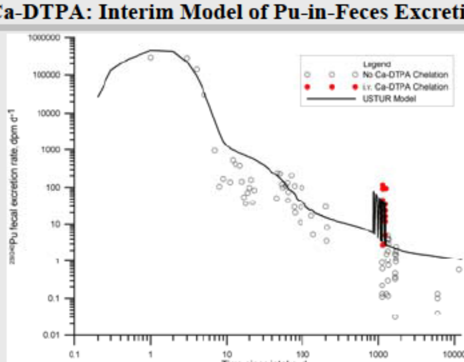
Ca-DTPA: Interim Model of Pu-in-Feces Excretion



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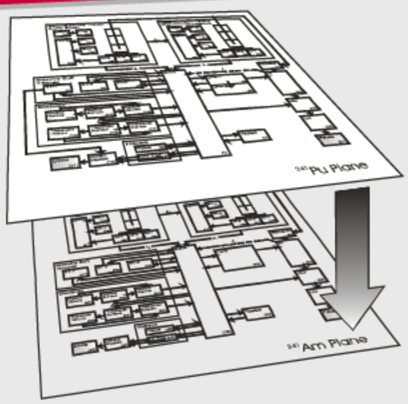
Case 0269: Interim USTUR Model Predictions

Tissue	Tissue Content, kBq		
	Measured	USTUR Model	
		Ca-EDTA + Ca-DTPA	Untreated
Whole Body	2.280	2.289	4.225
Lungs	0.0267	0.0267	0.0267
Lymph Nodes	0.00019	0.00021	0.00021
Liver	0.937	0.814	1.623
Skeleton	1.178	1.213	2.183
Muscle, Skin, *etc.*	0.141	0.228	0.383
Kidneys	0.00169	0.00166	0.00317

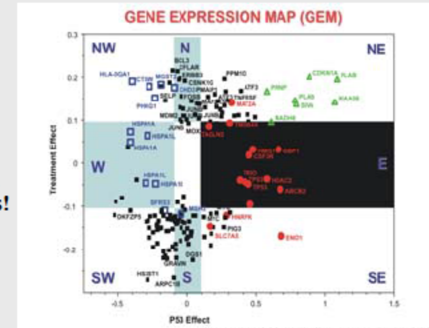
Future

Solve
Extended Rate Matrix
for USTUR Whole-Body Cases with Significant ^{241}Am in-growth



Future

It's All in the Genes!



Daoud et al. Cancer Res 63: 2782-93,2003

The Future – My Prediction!

- Greater confidence in the "accuracy" and predictive power of biokinetic models for the actinides.
- Understanding of the "variability" – and confidence bounds – of actinide tissue dose:
  - Including those to "other" organs – such as the brain and glandular organs
- ***"Pu" will contribute as much to the establishment of "realistic" (acceptable?) health protection standards for internal α-emitters as did "Ra" in the earliest days!!!***