出國報告（出國類別：實習）

赴美實習核醫藥物劑量評估公差報告

服務機關：核能研究所
姓名職稱：羅彩月
派赴國家：美國
出國期間：98 年 8 月 29 日~98 年 10 月 2 日
報告日期：98 年 10 月 30 日

摘　要

本次出國主要目的是爲學習核醫藥物之劑量評估，實習地點爲美國田納西州 Nashville 市 Vanderbilt University 附設醫學中心之 Department of Radiology and radiological science，Dr. Michael G. Stabin 目前任職於該部門，爲該校之副教授，實習課程分成下列單元，，分別爲: (1)Standard kinetic models and phantoms (2)Extrapolation of animal data (3)Bone marrow dosimetry discussion (4)Patient specific dosimetry discussion (5)Compartment modeling (6) Small scale and microdosimetry discussion (7)Image quantification—human data (8) Bone marrow dosimetry (9)Curve fitting and regression，並以本所之動物實驗數據及他的案例數據進行 OLINDA-EXM 軟體演練，期能與本領域之專家建立合作管道，有助於本所治療用核醫藥物研發之國際化。

目　　次

摘　要

（頁碼）

一、目 的

同位素組近年來積極投入治療用核醫藥物之研發，在肝癌與大腸癌之相關研究已有多項成果，配合藥物開發之時程，動物試驗後必須進入臨床試驗，本所目前之研究仍多侷限於動物試驗，如何如動物試驗之數據推估臨床試驗之劑量爲未來之重點。

Dr. Michael G. Stabin 爲美國 Vanderbilt University Medical Center 放射科學系副教授 (Associate Professor of Radiology and Radiological Sciences)，曾參與醫用體內輻射劑量評估軟體 MIRDOSE 之設計與執行，並設計 OLINDA 劑量評估軟體，該軟體爲唯一獲得美國 FDA 認證之劑量評估專用軟體。Dr. Stabin 發表多篇重要研究論文於核醫相關期刊，並撰寫多本專書，爲本領域之國際知名學者。本次出國主要目的即是向 Dr. Stabin 學習核醫藥物之劑量評估。實驗室學習相關理論基礎外，協助並輔導本所完成肝癌治療用核醫藥物之劑量評估及未來臨床劑量之設計，將對本所開發治療用核醫藥物之劑量選擇提供實質助益，亦能與本領域之專家建立合作管道，並有助於本所核醫藥物研發之國際化。

二、過 程

Date(mm/dd)	Project
8/29-8/30	去程(桃園至美國田納西州 Nashville city)
8/31	安頓行李及實習之住所
9/01	至 Vanderbilt University 拜訪 Dr. Stabin 報到，並至 Department of Radiology and Radiological Science 辦理報到手續及製作識別證事宜。(附件一)
9/02	與 Dr. Stabin 討論本次實習之主要目的以及後續實習之規畫。Dr. Stabin 提供論著 ”Fundamentals of Nuclear Medicine Dosimetry”，供作本次實習之研習教材。
09/03-9/04	OLINDA-EXM Software preparation and read information
09/07-09/11	(1)Kinetic modeling discussion (2)Standard kinetic models and phantoms (3)Extrapolation of animal data (4)Case study
09/14-09/18	(1)Bone marrow dosimetry discussion (2)Patient specific dosimetry discussion (3)Small scale and microdosimetry discussion (4)Case Study
09/21-09/25	(1)Curve fitting and regression (2)Compartment modeling (3)Animal data extrapolation (4)Case study
09/28-09/30	(1)Bone marrow dosimetry (2)Image quantification— human data (3)Case study and review
10/01-10/02	回程

三、心 得

醫用體內輻射吸收劑量(Medical Internal Radiation Absorbed Dose ，以下簡稱 MIRD)的評估對於核醫藥物應用於醫療之行爲不管是診斷或治療或生理代謝性研究等等都是必須的，對於新核醫藥物之開發而言，體內吸收劑量的計算更是必要的，依我國衛生署之“核醫放射性製劑之查驗登記”規定(附件二)，新藥之查驗登記必須檢附體內輻射劑量的評估數據。

核子醫學期刊上常見新核醫藥物之動物實驗皆會附上體內評估數據，這個資料之意義乃用於預估人體使用時之可能造成之體內劑量並決定人體可使用之放射活度，而第一階段人體臨床試驗(Phase I)所獲得核醫藥物之體內分佈數據則可用於評估人體的真正劑量，且因不同疾病而有不同之計算模式可供運用。美國核醫學會深刻體會體內輻射劑量評估之重要性，學會設有 MIRD Committee，專門負責發展及彙整人體使用之核種的體內吸收劑量。歐洲核醫學會(European Nuclear Medicine Association)也自 2004 年起於核醫學會年會特別成立了輻射劑量之專門分會(ISRTRD: Therapy and dosimetry)，提供全世界對體內輻射劑量評估有興趣的研究人員交流之機會。

吸收劑量意指游離輻射對有興趣之器官其每單位質量所釋出之能量，由於計算相當複雜，因此，美國橡樹嶺國家實驗室之 Radiation Internal Dose Information Center (RIDIC)乃針對一些最常遇到的難題利用一些簡單的基本運算將其簡化後，發展出一套專爲計算輻射體內劑量的軟體(MIRDOSE)，用於體內各器官之輻射吸收劑量之估計。2000 年 MIRDOSE 3 被發佈停止供應的消息，因爲 1998 年 RIDIC 配合血管近接治療發展之計畫，設計一套相當易於使用軟體可用於計畫放射源血管對血管壁所造成之劑量，因此被 FDA 認爲它是屬於 treatment planning device，因此，FDA 考慮” Whether MIRDOSE 3 should be classified a treatment planning device that required cleared premarketed notification 501(k).”

Dr. Michael G. Stabin 爲美國 Vanderbilt University Medical Center 放射科學系副教授(Associate Professor of Radiology and Radiological Sciences)，曾參與醫用體內輻射劑量評估軟體 MIRDOSE 之設計與執行，並設計 OLINDA 劑量評估軟體，Dr. Stabin 發表多篇重要研究論

文於核醫相關期刊，並撰寫多本專書，爲本領域之國際知名學者。Dr. Stabin 建立之 OLINDA/EXM 軟體具有特色包括: (1)Nearly 600 new radionuclides (including alpha emitters)(2)New organ phantoms(3)A revised and improved bone model(4)A code for performing kinetic analysis of biokinetic data(5)The ability to modify organ masses to patient-specific values，本軟體爲唯一獲得美國 FDA 認證之劑量評估專用軟體。

本次出差乃針對本所開發診療用核醫藥物之開發所需體內劑量之計算與應用，經與 Dr. Stabin 討論後，以他的論著"Fundamentals of Nuclear Medicine Dosimetry"當做研習教材，將實習課程分成下列單元，，分別爲: (1)Standard kinetic models and phantoms (2)Extrapolation of animal data (3)Bone marrow dosimetry discussion (4)Patient specific dosimetry discussion (5)Compartment modeling (6) Small scale and microdosimetry discussion (7)Image quantification—human data (8) Bone marrow dosimetry (9)Curve fitting and regression，並以本所之動物實驗數據及他的案例數據進行 OLINDA-EXM 軟體演練，學習之內容請參考附件三之簡報資料。

Dr. Stabin 在他的專書前言中提到他希望他的書可以提供核子醫學及輻射防護一有用的資訊，對他而言，這份工作的最大回饋是他所開發的東西可以成爲核醫例行應用的工具。雖然有人將自己辛苦設計的東西視爲珍寶，不願與人分享，尤其當他把他多年的研究心得集結成冊後，有人曾笑他傻，但他卻認爲『The open sharing of information in the scientific community leads to heighten understanding, thriving collaboration between like-minded investigators, the spawning of new ideas, and the growth and maturation of new investigators whose contributions end up benefiting us all』。由於其寬厚與開放之胸襟，當彩月提出實習申請時，Dr. Stabin 能應允接受，當彩月在該校實習期間，即使教學與研究工作相當煩忙，但 Dr. Stabin 仍每天撥出時段，安排與彩月進行教學演練，他最常引用的一句話是『The world can only be grasped by action, not by contemplation』(by Jacob Bronowski)，由於他的努力與執著，使其論著豐富，並接受全球核醫研發單位與藥廠之委託，協助進行動物實驗與人體臨床試驗之劑量評估，本次得以有機會向 Dr. Stabin 學習專業技術外，對未來本開發治療用核醫藥物之劑量評估及臨床試驗數據分析，亦

建立合作之管道。

實習期間，經由不斷討論與實例演練中，發現 OLINDA-EXM 雖爲目前全球公認之商業用體內劑量計算軟體，但在腫瘤劑量之計算上仍有其缺憾，Dr. Stabin 本軟體上設有 sphere model 可用於腫瘤劑量計算，但由於其假體(phantom)皆以正常人的器官做設計模型，sphere model 僅針對該腫瘤區域之局部劑量，無法針對其它器官之影響做評估，對此，Dr. Stabin 表示對診斷用核醫藥物而言，核醫藥物在腫瘤的分佈百分比不高，對全身劑量之計算影響不大，但對於未來投與高劑量之治療用核醫藥物，或者採用局部給藥方式之治療用核醫藥物而言，sphere model 能提供之劑量評估助益有限，在此條件下，他必須配合 Monte Carlo 軟體之使用(例如 MCNP 及 EGS4 等 radiation transport code)，評估腫瘤之位置與其它器官之距離，再加以計算正確之劑量，尤其是配合臨床影像評估之技術，目前有多所學校開發出一些計算方法，例如 Memorial Sloan-Kettering Cancer center 計計 3D-ID 軟體、University of Lund 之 SIMOS 軟體以及 City of Hope medical Center 之 RTDS 軟體等，但上述軟體皆屬於測試階段，仍未被確認其實用性，Dr. Stabin 表示他的實驗室正在努力提升 OLINDA-EXM 的計算功能，目前限於經費與人力，仍未有具體成果，未來則希望相關軟體完成設計後，亦能向 FDA 取得認證，使核醫界都能方便應用這些軟體。

Universityof Vanderbilt 是一所歷史悠久的大學，自 1877 年設立以來，已有兩百年以上的歷史，其附設之 medical center 依據 2009 年 US News 最新發佈之評估報告『America's Best Hospitals: the 2009–10 Honor Roll』，Vanderbilt University Medical Center 排名全美醫院之第十六名(附件四)，該院目前有二千多名員工，爲田納西州及中南部各州相當重要之醫療機構。

實習期間曾與 Dr. Stabin 該院核醫科(設於 Department of radiology and radiological science)參訪，該科設有 cyclotron(GE 公司)一台，由放射藥師及其它工作工員例行提供該院臨床地區之醫院所需 PET 核醫藥物，SPECT 所需藥物皆由簽約核醫藥局調劑後供應臨床使用，Dr. Stabin 表示雖然體內劑量之計算對核醫藥物之臨床應用相當重要，但目前核醫科醫師在使用核醫藥物時，仍依藥廠提供之建議劑量執行造影，即使目前已在臨床使用之治療用核醫藥物 I-131 Bexxar 亦未針對每一個病患尋找最適量化劑量，醫師大多給予相對保守之治療劑量，

導致療效有限，反觀，臨床放射腫瘤科之治療劑量評估技術已相對成熟，每一位病人接受治療之前皆會先用軟體加以評估後再讓病人接受放射治療。比對核醫與放療兩個相似的治療領域，卻有此差別，一方面也是治療用核醫藥物之開發仍不普及，再者相關軟體之設計仍未完成，導致臨床醫師即使想用，亦無法取得合適之工具，Dr. Stabin 希望軟體設計再搭配治療用核醫藥物之開發，兩者相輔相成，共同提供病患之最佳治療選擇。

四、建 議 事 項

有鑑於本所積極投入之治療用核醫藥物開發，目前有多項藥品在動物試驗階段皆顯示其治療之應用潛力，國內有多家研究機構亦從事新藥之開發研究，如果從事新藥之開發則一定需要體內輻射劑量評估之數據，動物實驗之數據雖可提供 臨床之參考，但仍需以健康受試者進行劑量評估，才能決定第二階段及第三階段病人之劑量範圍。尤其未來臨床之劑量評估涉及影像分析，此部份尤須專業人員協助，謹就出國學習之心得提出下列之建議，以供未來本所相關規畫之參考:

一、 國外有關於治療用核醫藥物之劑量評估仍未完整，OLINDA-EXM 較適合診斷用核醫藥物之劑量評估，本所保健物理組熟稔蒙地卡羅軟體之應用研究，建議未來可以著力於本方面之研究，如果本所能結合 Dr. Stabin 之專長，共同合作致力於治療用核醫藥物劑量評估軟體之開發，屆時不僅成果共享，且能臨床方便應用，提供病患之劑量評估工具，不僅提升病患之疾病治癒率，且能加速治療用核醫藥物之開發與應用，造福大眾。

二、 目前國內各大研究機構積極投入新核醫藥物之開發，體內射劑量評估數據是臨床試驗或新藥查驗登記必須提供之安全性數據之一，雖然各個實驗室可以分別購得 OLINDA/EXM 軟體，但數據正確與否則未有評估機制，核研所爲國家級之核能專業實驗室，不論技術與能力皆領先其它研究單位，因此，建議本所可以建立輻射評估專業實驗室，協助國內其它單位執行相關計算與評估。

三、 建立與 Dr. Stabin 之合作管道，協助本所在治療用核醫藥物評估技術之建立，尤其是未來在臨床試驗之規畫與執行時，如能獲得其協助，則對未來劑量評估數據之可靠性更具公信力。

四、 依據 Dr. Stabin 之經驗，目前對於 SPECT 或 PET 影像之 ROI 圈選皆需以人力執行之，造成影像劑量評估之技術瓶頸，本所物理組已建立 microCT 影像之自動圈選

技術，建議應積極擴大其應用領域，協助臨床影像 ROI 圈選之自動化作業，則對射劑量評估亦大有助益。

五、 附 錄

附件一


Michael G. Stabin
Fundamentals of Nuclear Medicine Dosimetry
Tsa-Yueh Luo , PhD
Radiology
Visiting Professor
Visitor
Vanderbilt
University
Medical Center

附件二

核醫放射性藥品新藥、新劑型、新劑量查驗登記應檢附之技術性資料表

申請核醫新藥查驗登記應檢附資料	文件類別		起源發現之經過及使用情形	物理性質及化學性質之檢驗方法及檢驗規格			非臨床動物試驗報告								臨床試驗報告(應裝訂成冊並摘要乙份)		輻射劑量學報告	國外採用證明	安定性試驗報告
							安全性試驗報告					藥效試驗	藥動試驗						
	藥品資料/新藥類別		起源發現經過	構造式物理化學性質	檢驗規格及方法	溶離試驗含量均一度試驗	或提供對照標準品提供新成份之原料藥品	單一劑量毒性試驗	重覆劑量毒性試驗	抗原性試驗	局部刺激性試驗致突變性、致癌性試驗胚胎試驗、依賴性試驗	輻射生物試驗	證明有效之試驗	一般藥理試驗	代謝、排泄、吸收、分佈、	生體相等性試驗生體可用率試驗	臨床試驗之設計及結果	研究文獻之回顧及出處		
	新成分	診斷用	○	○	○	△	○	○	△	△	╳	╳	○	╳	○	╳	○	○	○	○
		治療用	○	○	○	△	○	○	△	△	△	○	○	△	○	╳	○	○	○	○
	新使用途徑		○	╳	○	△	╳	╳	╳	╳	╳	╳	╳	╳	△	△	△	△	○	○
	新適應症		○	╳	○	╳	╳	╳	╳	╳	╳	╳	○	╳	╳	╳	△	△	○	○
核醫新劑型、新劑量查驗登記應檢附資料	新劑型		○	╳	○	△	╳	╳	╳	╳	╳	╳	╳	╳	△	△	△	△	○	○
	新劑量		○	╳	○	╳	╳	╳	╳	╳	╳	╳	╳	╳	╳	╳	△	△	○	○

○：表示須檢附該項目之資料。 ╳：表示不須檢附該項目之資料。△：表示視個案而檢附該項目之資料。

附件 三

Internal Radiation Dosimetry

羅彩月

98.10.13

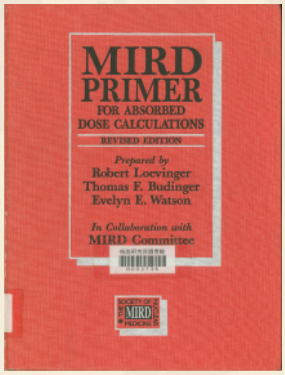
1

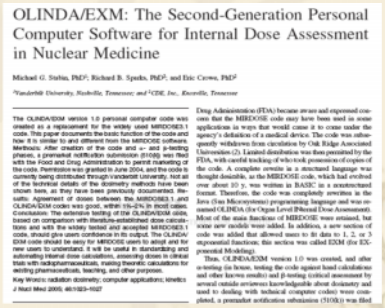
Introduction

- **Absorbed-dose calculation**: evaluation of the risks involved in the application of radiopharmaceuticals to medical studies, whether they may be imaging, therapy, or noninvasive physiologic and metabolic studies.
- **Absorbed dose**: the amount of energy from ionization radiation that is deposited per unit mass at the site of interest.

2

Medical Internal Radiation Dosimetry (MIRD)




OLINDA/EXM: The Second-Generation Personal Computer Software for Internal Dose Assessment in Nuclear Medicine

1

Concepts

- Internal dose estimates – “marriage” of physical and biological quantities
- Biology – distribution and kinetics
- Physics – energy deposition patterns

4

$$D_{r_k} = \sum_h \tilde{A}_h S(r_k \leftarrow r_h)$$

r_h : Source region r_k : Target region $\tilde{A}$: cumulated activity

$$S(r_k \leftarrow r_h) = \frac{k \sum_i n_i E_i \phi_i (r_k \leftarrow r_h)}{m_{r_k}}$$

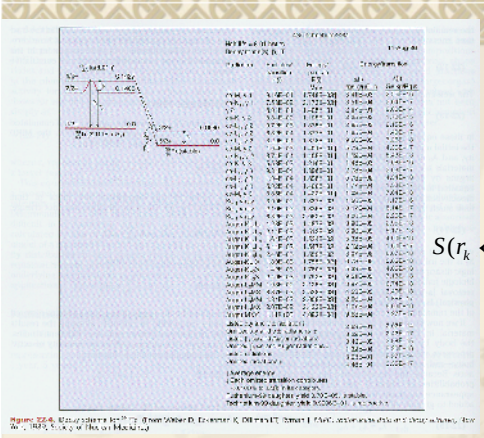
n: the number of radiation with energy E emitted per nuclear transition

Ø: the fraction of energy emitted that is absorbed in the target

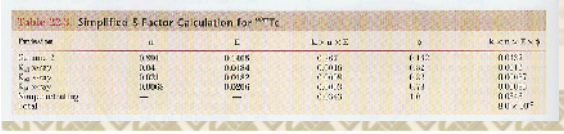
m: the mass of the target region

k: proportionality constant (rad-g/μCi-hr-MeV) or Gy-kg/MBq-sec-MeV)

5



$$S(r_k \leftarrow r_h) = \frac{k \sum_i n_i E_i \phi_i (r_k \leftarrow r_h)}{m_{r_k}}$$



6

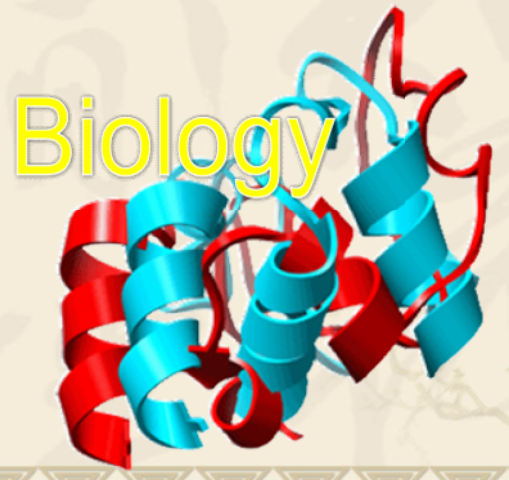
Absorbed dose: $D = \frac{d\varepsilon}{dm}$

$$D = N \times DCF$$

N is the number of disintegrations that occur in a source region

DCF is the dose conversion factor, which gives the dose absorbed in a target per disintegration in a source

7



8

Determination of Kinetic Data

- Preclinical:
  - Choice of animal species
  - Choice of analytical method
  - Execution of experiments
  - Extrapolation of results
  - Kinetic analysis
- Clinical:
  - Execution of experiments
  - Kinetic analysis

9

Animal Data Collection Methods

- Autoradiography
- Necropsy
- Imaging
  - microPET and microSPECT methods
    - Region of Interest (ROI) analysis of images, as in humans.

10

Animal Data Extrapolation Methods

- Direct Use (i.e. no extrapolation)
  - %/organ in the animal = %/organ in the human
- Concentration equivalence
  - %/g in animal = %/g in human
- Concentration/Body weight equivalence
  - % - kg/g in animal = % - kg/g in human
  - (organ mass in g)/(body weight in kg) used as scaling factor.

11

Mass scaling

$$\left(\frac{\%}{g}\right) \times body\ \ mass\ \ (kg) \equiv \frac{\% - kg}{g} \quad \leftarrow \text{Animal}$$

$$\frac{\% - kg}{g} \times \frac{organ\ \ mass\ \ (g)}{body\ \ mass\ \ (kg)} \equiv \frac{\%}{organ} \quad \leftarrow \text{Human}$$

Mass and time scaling

$$t_a = t_h \left[\frac{m_h}{m_a}\right]^{0.25}$$

12

	Average	Average	Average
	5'	45'	90'
	%ID-kg/g	%ID-kg/g	%ID-kg/g
Blood	0	0	0
Heart	0.0696	0.0193	0.0127
total lung	0.1185	0.0349	0.0270
total liver	0.5753	0.2376	0.0742
spleen	0.1002	0.0486	0.0422
total kidney	0.2753	0.2678	0.1604
small intest up	0.0000	0.0000	0.0000
small intest low	0.0000	0.0000	0.0000
total small inst	0.2286	0.5488	0.2736
large intest	0.0830	0.0261	0.0234
stomach	0.0929	0.0238	0.0203
muscle	0.0000	0.0000	0.0000
total skin	0.0000	0.0000	0.0000
Testes	0.0595	0.0585	0.0324
brain	0.1836	0.0308	0.0085
bone	0.0426	0.0249	0.0225

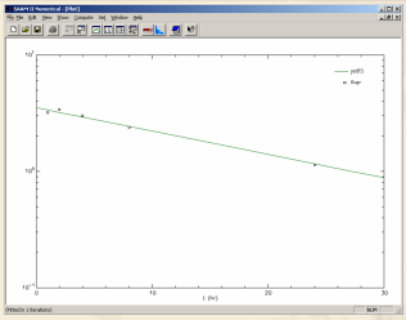
% kg/g extrapolation → Human %/organ

1

		Average	Average	Average
		5'	45'	90'
		%/organ-hum	%/organ-hum	%/organ-hum
Blood				
Heart	316	0.298	0.083	0.054
total lung	1000	1.607	0.473	0.367
total liver	1910	14.909	6.158	1.922
spleen	183	0.249	0.121	0.105
total kidney	299	1.117	1.087	0.651
small intest up		0.000	0.000	0.000
small intest low		0.000	0.000	0.000
total small inst	600	1.861	4.468	2.227
large intest	387	0.436	0.137	0.123
stomach	158	0.199	0.051	0.043
muscle				
total skin				
Testes	39	0.032	0.031	0.017
brain	1420	3.538	0.594	0.164
bone	5000	2.891	1.692	1.527

Select important organs to fit

14



$$A(t) = A_1 e^{-a_1 t} + A_2 e^{-a_2 t} + \cdots$$

$$N = \int_0^\infty A_i e^{-a_i t}\, dt = \frac{A_i}{a_i} = 1.443 \times A_i \times T_{1/2_i}$$

15

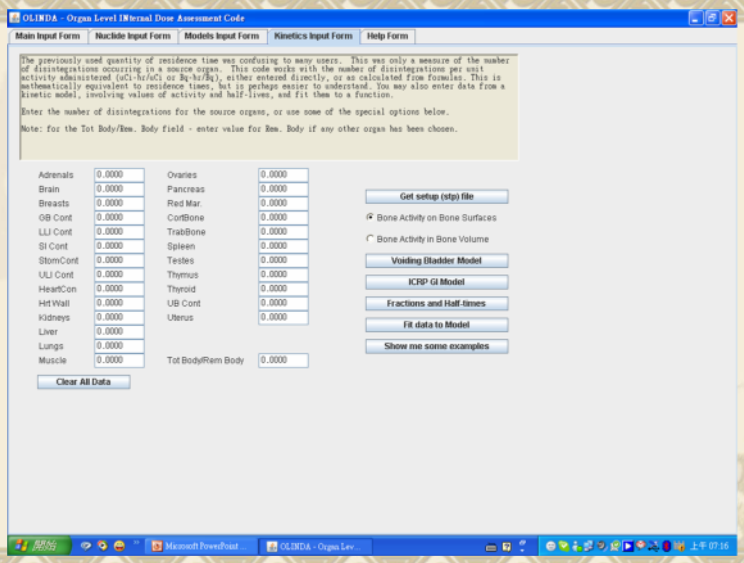
λ_p =	2.0382	h^{-1}	
A_1	a_1	N (Bq-h/Bq)	
1.2928	1.0034	0.0043	total lung
17.2616	1.4468	0.0495	total liver
0.2282	0.6051	0.0009	spleen
1.2254	0.3854	0.0051	total kidney
3.5862	2.1509	0.0086	brain
			bone
		0.42236	RB

$$N_{TB}=\frac{1}{\lambda_{phys}}$$

$$N_{RB}=N_{TB}-\sum N_{organs}$$

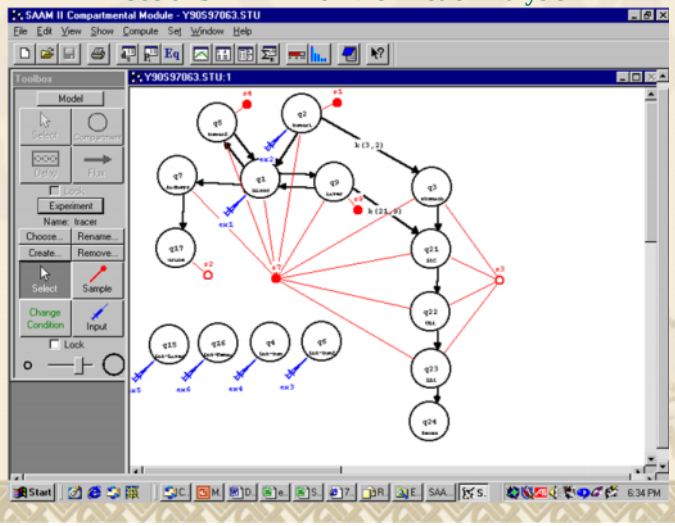
Assumption: all activity retained in body, activity not in organs uniformly in all other tissues.

16



Compartmental Analysis

Use of SAAM II for Biokinetic Analysis



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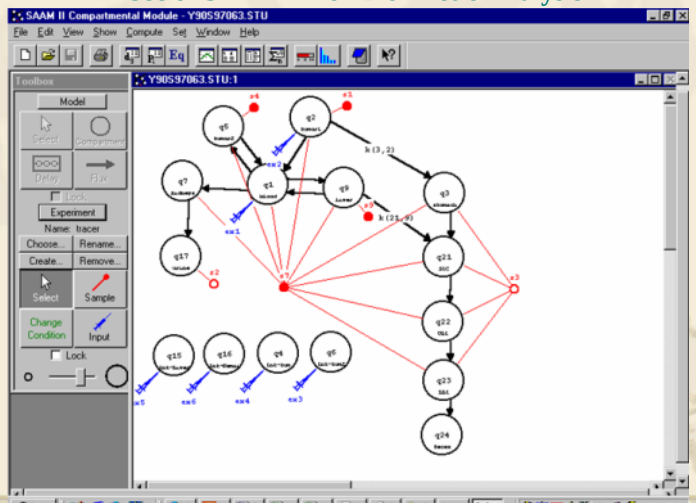
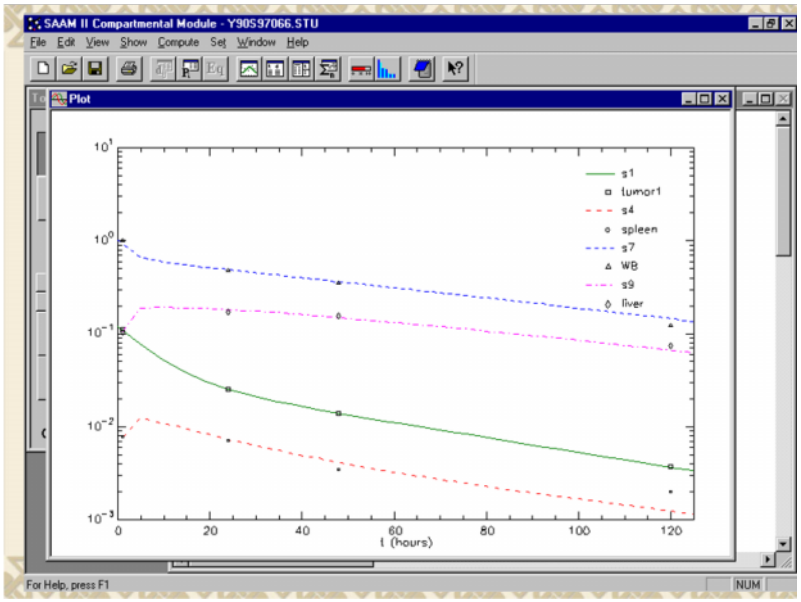
Compartmental Analysis

Use of SAAM II for Biokinetic Analysis



18



Acquisition of Kinetic Data
Human Studies

- Gamma camera – setup, calibration, quality control issues
- Choice of regions of interest
- Number and spacing of data points
- Treatment of kinetic data
  - Kinetic model form, parameters
  - Application to dose calculation models

20

Gamma Camera Data: Activity Calibration Factor

- Geometric mean method, in principle, removes depth dependence.

$$A_{ROI} = \sqrt{\frac{I_A I_P}{e^{-\mu_e t}}} \frac{f_j}{C}$$

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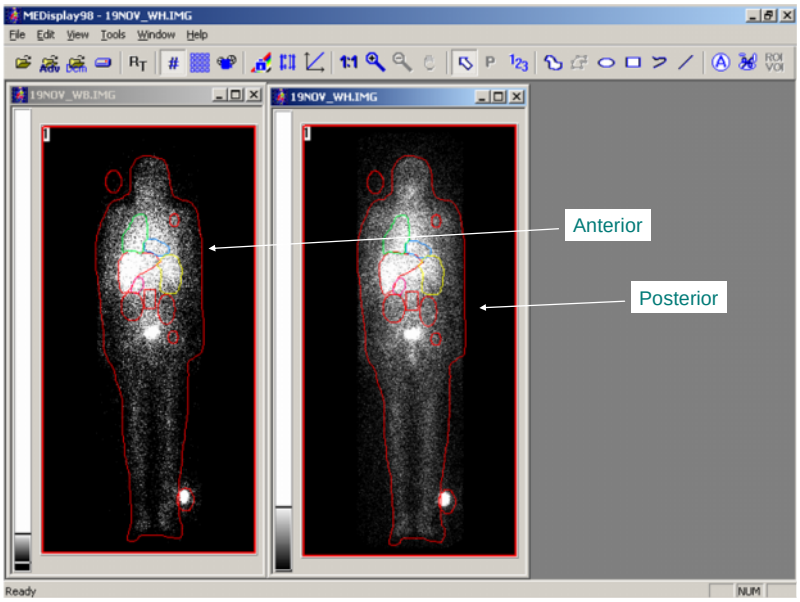
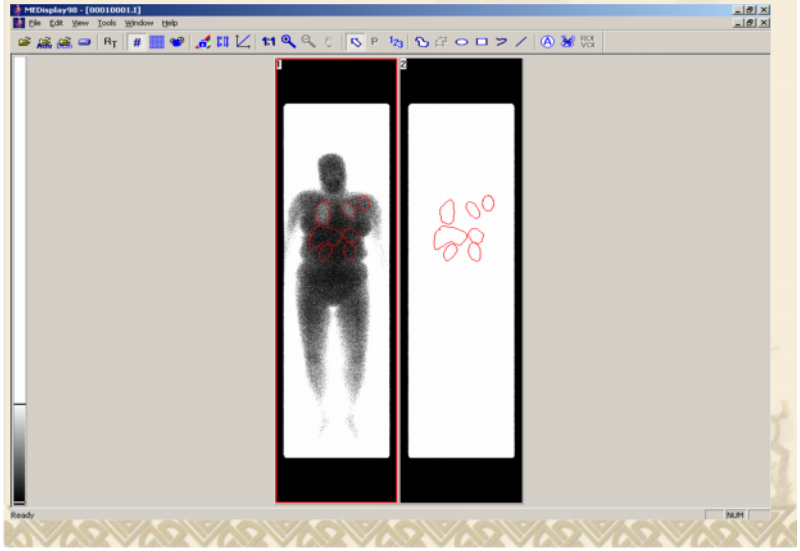
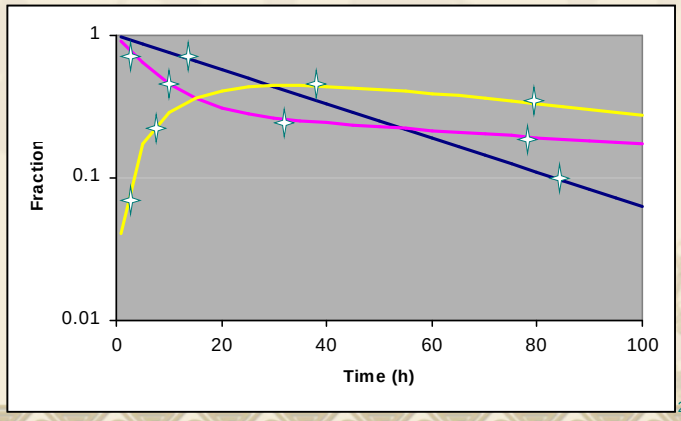


Co-57 Transmission Scan – Attenuation Correction



Metabolic Models: Patient-specific kinetic modeling

MIRD 16: Number and spacing of time points



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Acquisition of Kinetic Data Human Studies

- Gamma camera – setup, calibration, quality control issues
- Choice of regions of interest
- Number and spacing of data points
- Treatment of kinetic data
  - Kinetic model form, parameters
  - Application to dose calculation models

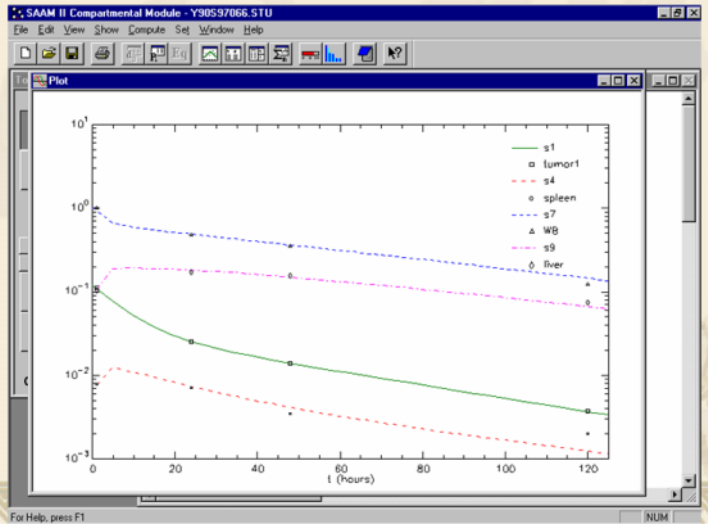
20

Gamma Camera Data: Activity Calibration Factor

- Geometric mean method, in principle, removes depth dependence.

$$A_{ROI} = \sqrt{\frac{I_A I_P}{e^{-\mu_e t}}} \frac{f_j}{C}$$

21



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Area under any time-activity curve:

Number of disintegrations occurring in the source region

Units: Bq-hr, Bq-s, μCi-hr, etc.

Also: Bq-hr/Bq (administered), Bq-s/Bq, μCi-hr/μCi, etc.

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RADAR Dose Factors

- We have calculated dose factors for our >800 radionuclides for:

Adult Male	Adult Female
15-year-old	3 month pregnant female
10-year-old	6 month pregnant female
5-year-old	9 month pregnant female
1-year-old	MIRD Head and Brain Model
Newborn	Prostate Gland Model
Unit Density Sphere Model	Peritoneal Cavity Model

- Get the data free, by electronic download, at our site.

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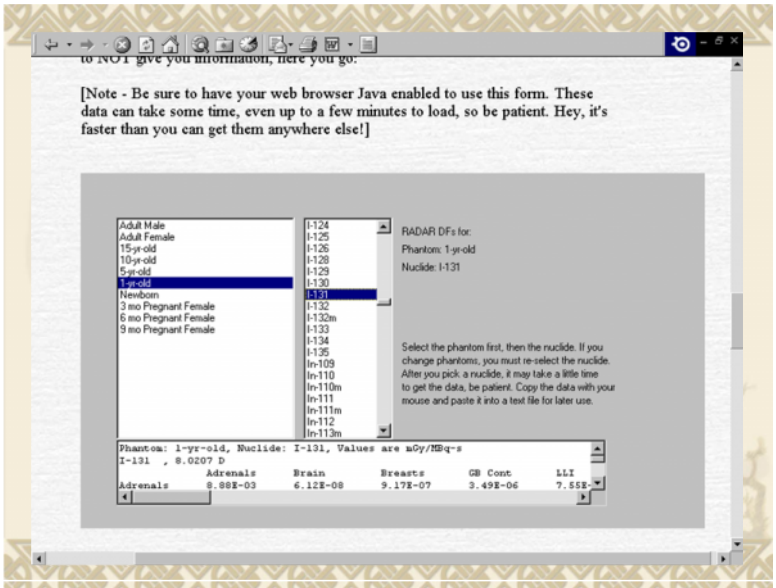

Software Tools: Nuclear Medicine Internal Dosimetry

- MIRDOSE →OLINDA/EXM
  - Best available dose models (adults, children, pregnant women)
  - Standardization of dose calculations
    - Target organs
    - Remainder of body correction
    - Marrow models
    - Organ mass adjustments

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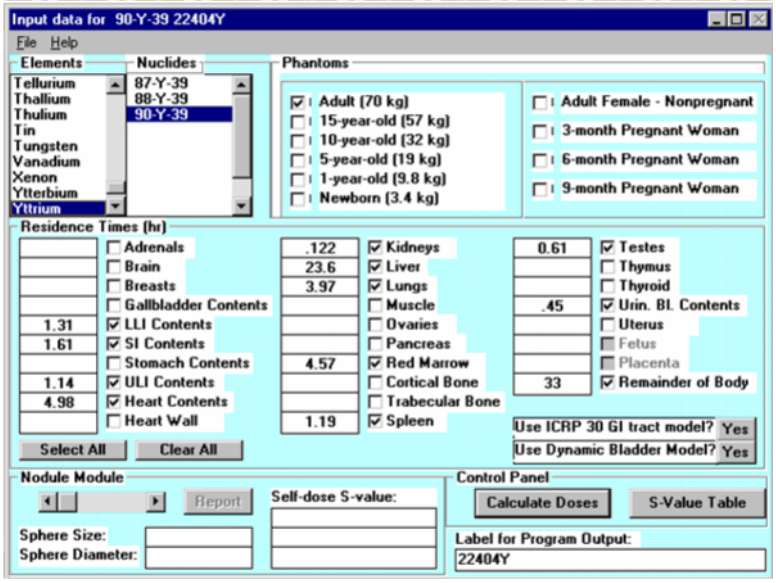
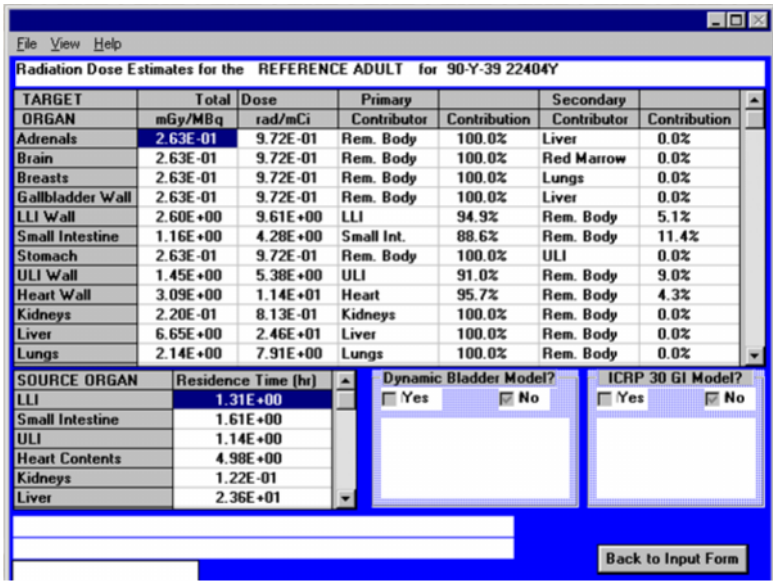
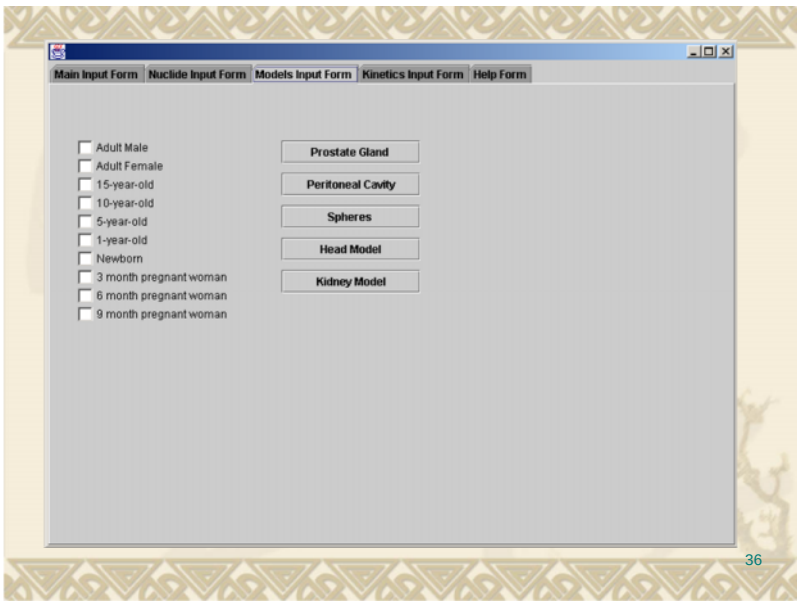
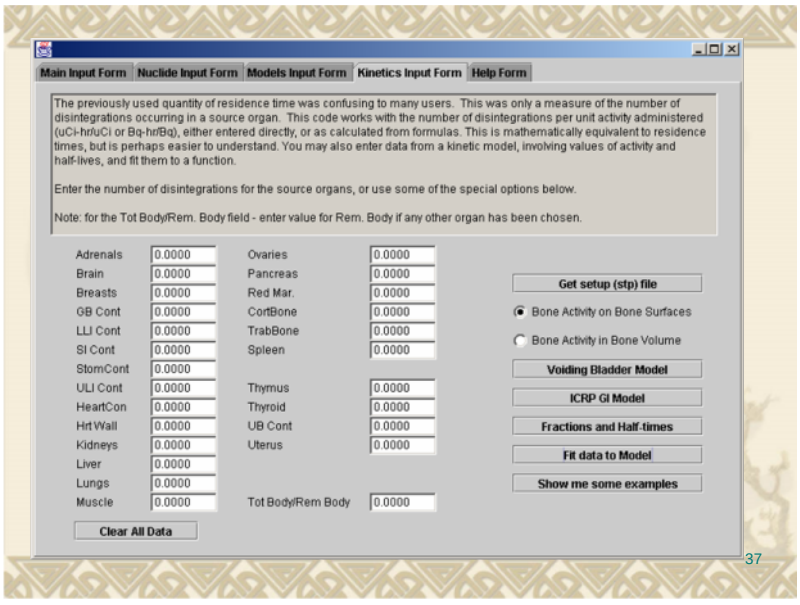
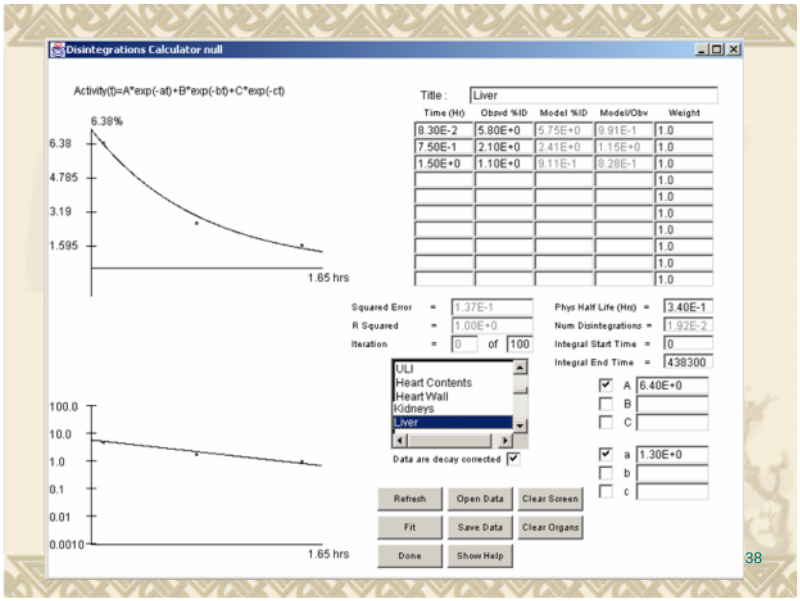



File View Help
Radiation Dose Estimates for the REFERENCE ADULT for 90-Y-39 22404Y
TARGET ORGAN | Total Dose mGy/MBq | rad/mCi | Primary Contributor | Contribution | Secondary Contributor | Contribution
Adrenals 2.63E-01 9.72E-01 Rem. Body 100.0% Liver 0.0%
Brain 2.63E-01 9.72E-01 Rem. Body 100.0% Red Marrow 0.0%
Breasts 2.63E-01 9.72E-01 Rem. Body 100.0% Lungs 0.0%
Gallbladder Wall 2.63E-01 9.72E-01 Rem. Body 100.0% Liver 0.0%
LLI Wall 2.60E+00 9.61E+00 LLI 94.9% Rem. Body 5.1%
Small Intestine 1.16E+00 4.28E+00 Small Int. 88.6% Rem. Body 11.4%
Stomach 2.63E-01 9.72E-01 Rem. Body 100.0% ULI 0.0%
ULI Wall 1.45E+00 5.38E+00 ULI 91.0% Rem. Body 9.0%
Heart Wall 3.09E+00 1.14E+01 Heart 95.7% Rem. Body 4.3%
Kidneys 2.20E-01 8.13E-01 Kidneys 100.0% Rem. Body 0.0%
Liver 6.65E+00 2.46E+01 Liver 100.0% Rem. Body 0.0%
Lungs 2.14E+00 7.91E+00 Lungs 100.0% Rem. Body 0.0%
SOURCE ORGAN | Residence Time (hr)
LLI 1.31E+00
Small Intestine 1.61E+00
ULI 1.14E+00
Heart Contents 4.98E+00
Kidneys 1.22E-01
Liver 2.36E+01
Dynamic Bladder Model? Yes No
ICRP 30 GI Model? Yes No
Back to Input Form


Main Input Form
Nuclide Input Form
Models Input Form
Kinetics Input Form
Help Form
Adult Male
Adult Female
15-year-old
10-year-old
5-year-old
1-year-old
Newborn
3 month pregnant woman
6 month pregnant woman
9 month pregnant woman
Prostate Gland
Peritoneal Cavity
Spheres
Head Model
Kidney Model
36


Main Input Form
Nuclide Input Form
Models Input Form
Kinetics Input Form
Help Form
The previously used quantity of residence time was confusing to many users. This was only a measure of the number of disintegrations occurring in a source organ. This code works with the number of disintegrations per unit activity administered (uCi-hr/uCi or Bq-hr/Bq), either entered directly, or as calculated from formulas. This is mathematically equivalent to residence times, but is perhaps easier to understand. You may also enter data from a kinetic model, involving values of activity and half-lives, and fit them to a function.
Enter the number of disintegrations for the source organs, or use some of the special options below.
Note: for the Tot Body/Rem. Body field - enter value for Rem. Body if any other organ has been chosen.
Adrenals 0.0000
Brain 0.0000
Breasts 0.0000
GB Cont 0.0000
LLI Cont 0.0000
SI Cont 0.0000
StomCont 0.0000
ULI Cont 0.0000
HeartCon 0.0000
Hrt Wall 0.0000
Kidneys 0.0000
Liver 0.0000
Lungs 0.0000
Muscle 0.0000
Ovaries 0.0000
Pancreas 0.0000
Red Mar. 0.0000
CortBone 0.0000
TrabBone 0.0000
Spleen 0.0000
Thymus 0.0000
Thyroid 0.0000
UB Cont 0.0000
Uterus 0.0000
Tot Body/Rem Body 0.0000
Clear All Data
Get setup (stp) file
Bone Activity on Bone Surfaces
Bone Activity in Bone Volume
Voiding Bladder Model
ICRP GI Model
Fractions and Half-times
Fit data to Model
Show me some examples
37


Disintegrations Calculator null
Activity(t)=A*exp(-at)+B*exp(-bt)+C*exp(-ct)
6.38%
6.38
4.785
3.19
1.595
1.65 hrs
100.0
10.0
1.0
0.1
0.01
0.0010
1.65 hrs
Title : Liver
Time (Hr) Obsvd %ID Model %ID Model/Obv Weight
8.30E-2 5.80E+0 5.75E+0 9.91E-1 1.0
7.50E-1 2.10E+0 2.41E+0 1.15E+0 1.0
1.50E+0 1.10E+0 9.11E-1 8.28E-1 1.0
Squared Error = 1.37E-1
R Squared = 1.00E+0
Iteration = 0 of 100
Phys Half Life (Hr) = 3.40E-1
Num Disintegrations = 1.92E-2
Integral Start Time = 0
Integral End Time = 438300
ULI
Heart Contents
Heart Wall
Kidneys
Liver
A 6.40E+0
B
C
a 1.30E+0
b
c
Data are decay corrected
Refresh
Open Data
Clear Screen
Fit
Save Data
Clear Organs
Done
Show Help

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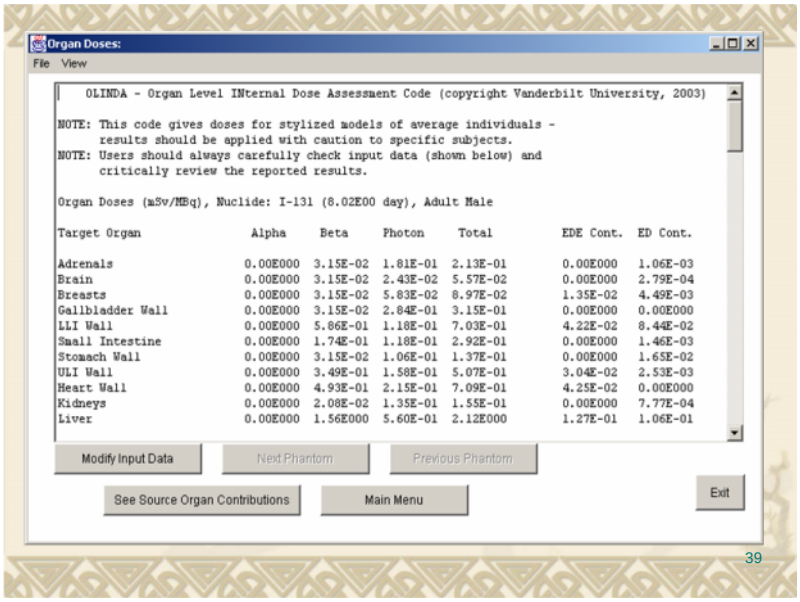
Organ Doses:
File View
OLINDA - Organ Level INternal Dose Assessment Code (copyright Vanderbilt University, 2003)
NOTE: This code gives doses for stylized models of average individuals -
results should be applied with caution to specific subjects.
NOTE: Users should always carefully check input data (shown below) and
critically review the reported results.
Organ Doses (mSv/MBq), Nuclide: I-131 (8.02E00 day), Adult Male
Target Organ Alpha Beta Photon Total EDE Cont. ED Cont.
Adrenals 0.00E000 3.15E-02 1.81E-01 2.13E-01 0.00E000 1.06E-03
Brain 0.00E000 3.15E-02 2.43E-02 5.57E-02 0.00E000 2.79E-04
Breasts 0.00E000 3.15E-02 5.83E-02 8.97E-02 1.35E-02 4.49E-03
Gallbladder Wall 0.00E000 3.15E-02 2.84E-01 3.15E-01 0.00E000 0.00E000
LLI Wall 0.00E000 5.86E-01 1.18E-01 7.03E-01 4.22E-02 8.44E-02
Small Intestine 0.00E000 1.74E-01 1.18E-01 2.92E-01 0.00E000 1.46E-03
Stomach Wall 0.00E000 3.15E-02 1.06E-01 1.37E-01 0.00E000 1.65E-02
ULI Wall 0.00E000 3.49E-01 1.58E-01 5.07E-01 3.04E-02 2.53E-03
Heart Wall 0.00E000 4.93E-01 2.15E-01 7.09E-01 4.25E-02 0.00E000
Kidneys 0.00E000 2.08E-02 1.35E-01 1.55E-01 0.00E000 7.77E-04
Liver 0.00E000 1.56E000 5.60E-01 2.12E000 1.27E-01 1.06E-01
Modify Input Data
Next Phantom
Previous Phantom
See Source Organ Contributions
Main Menu
Exit

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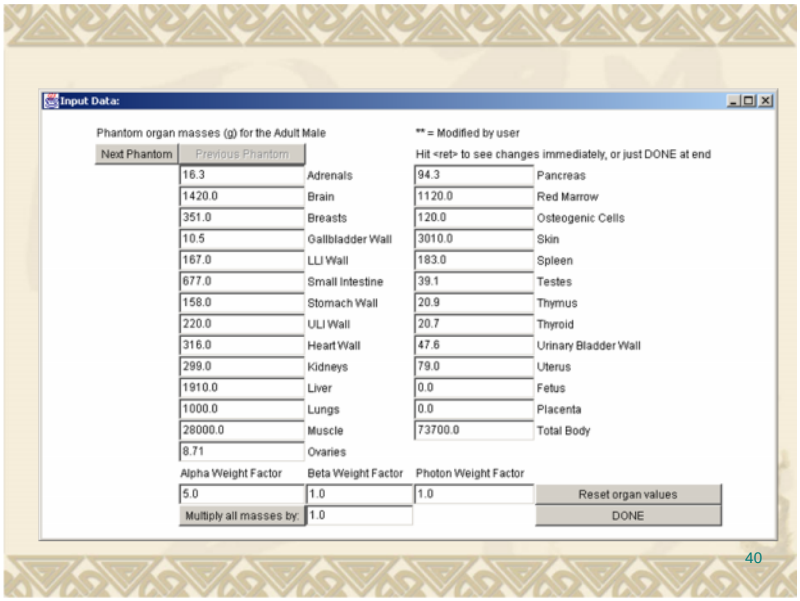
Input Data:
Phantom organ masses (g) for the Adult Male
** = Modified by user
Next Phantom
Previous Phantom
Hit <ret> to see changes immediately, or just DONE at end
16.3 Adrenals 94.3 Pancreas
1420.0 Brain 1120.0 Red Marrow
351.0 Breasts 120.0 Osteogenic Cells
10.5 Gallbladder Wall 3010.0 Skin
167.0 LLI Wall 183.0 Spleen
677.0 Small Intestine 39.1 Testes
158.0 Stomach Wall 20.9 Thymus
220.0 ULI Wall 20.7 Thyroid
316.0 Heart Wall 47.6 Urinary Bladder Wall
299.0 Kidneys 79.0 Uterus
1910.0 Liver 0.0 Fetus
1000.0 Lungs 0.0 Placenta
28000.0 Muscle 73700.0 Total Body
8.71 Ovaries
Alpha Weight Factor
Beta Weight Factor
Photon Weight Factor
5.0
1.0
1.0
Reset organ values
Multiply all masses by:
1.0
DONE

40

TABLE 1
Portion of Sample Output from OLINDA/EXM 1.0

Organ	Dose to target organs* α	β	Photon	Total	No. disintegrations in source organs†
Adrenals	0.00E+00	4.38E−02	8.05E−02	1.24E−01	
Brain	0.00E+00	4.38E−02	2.64E−02	7.32E−02	
Breasts	0.00E+00	4.38E−02	2.64E−02	7.22E−02	
Gallbladder wall	0.00E+00	4.38E−02	6.14E−02	1.05E−01	
Lower large intestine wall	0.00E+00	4.00E−02	6.02E−02	1.04E−01	
Small intestine	0.00E+00	4.38E−02	6.00E−02	1.06E−01	
Stomach wall	0.00E+00	4.38E−02	6.70E−02	1.11E−01	
Upper large intestine wall	0.00E+00	4.38E−02	5.78E−02	1.02E−01	
Heart wall	0.00E+00	4.38E−02	5.07E−02	9.46E−02	
Kidneys	0.00E+00	1.30E+00	2.40E−01	1.54E+00	3.50E+00
Liver	0.00E+00	2.61E−02	4.70E−02	7.32E−02	4.50E−01
Lungs	0.00E+00	1.33E−01	4.64E−02	1.83E−01	1.20E+00
Muscle	0.00E+00	4.38E−02	4.25E−02	8.64E−02	
Ovaries	0.00E+00	4.38E−02	6.74E−02	1.06E−01	
Pancreas	0.00E+00	4.38E−02	9.25E−02	1.37E−01	
Red marrow	0.00E+00	1.00E−01	5.67E−02	1.60E−01	1.50E+00
Osteogenic cells	0.00E+00	1.52E−01	5.52E−02	2.07E−01	
Skin	0.00E+00	4.38E−02	2.54E−02	6.92E−02	
Spleen	0.00E+00	1.33E+00	2.73E−01	1.61E+00	2.20E+00
Testes	0.00E+00	4.38E−02	4.04E−02	8.42E−02	
Thymus	0.00E+00	4.38E−02	4.07E−02	8.45E−02	
Thyroid	0.00E+00	4.38E−02	3.81E−02	8.19E−02	
Urinary bladder contents					1.98E+00
Urinary bladder wall	0.00E+00	5.64E−01	1.51E−01	7.15E−01	
Uterus	0.00E+00	4.38E−02	7.45E−02	1.18E−01	
Total body	0.00E+00	5.75E−02	4.41E−02	1.02E−01	
Remainder					2.81E+01

*mSv/MBq; nuclide, ^{131}I (8.02E0C day); adult male.
†MBq-h/MBq (μCi-h/μCi).

Example Consider the following data set.

Time (hr)	Activity (μ Ci)
0	100
0.5	72
1	35
2	24
4	20
6	15
10	12

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Trapezoidal Method

$$A = \sum_i \frac{(x_i + x_{i+1})}{2} \Delta t$$

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Trapezoidal Method: Each interval is treated separately, and the parts are added:

A1 = (100 + 72) * 0.5/2 = 43 μCi-hr
A2 = (72 + 35) * 0.5/2 = 26.75 μCi-hr
A3 = (35 + 24) * 1.0/2 = 29.5 μCi-hr
A4 = (24 + 20) * 2.0/2 = 44 μCi-hr
A5 = (20 + 15) * 2.0/2 = 35 μCi-hr
A6 = (15 + 12) * 4.0/2 = 54 μCi-hr
Total = 232 μCi-hr

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Least Squares Analysis –

In general, the approach is to minimize the sum of the squared distance of the data points from the fitted curve. The curve will have the form:

$$A(t) = a_1 \exp(-\lambda_1 t) + a_2 \exp(-\lambda_2 t) + \ldots$$

$$\int_0^\infty A(t)\,dt = \frac{a_1}{\lambda_1} + \frac{a_2}{\lambda_2} + \cdots$$

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For the above example, a computer fit of the data yielded the following fit:

$A(t) = 18.6 \exp(-0.039t) + 81.4 \exp(-1.23t)$

(Time was given in hours; therfore the units on the rate constants are hr^{-1}. The activity units are μCi.) The cumulative activity for this system, integrating from zero to infinity, then is:

Ã= 18.6/0.039 + 81.4/1.23 = 477 + 66 = 543 μCi-hr

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This does not agree well with the estimate given by the trapezoidal method. The reason for this is that this integration goes from zero to infinity and the trapezoidal method estimates cut off the integration at t=10 hours. Evidently, a significant amount of the area under the curve (about half!) exists beyond t=10 hours. So this shows the importance of estimating the area under the curve beyond the end of the data set.

$$N = \int_0^{\infty} A_i e^{-a_i t}\, dt = \frac{A_i}{a_i} = 1.443 \times A_i \times T_{1/2_i}$$

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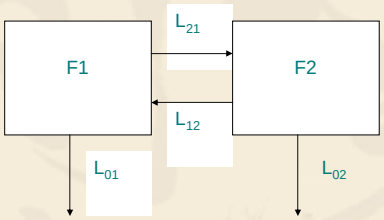

48

$$\frac{dF_1(t)}{dt} = -(L_{01} + L_{21})F_1(t) + L_{12}F_2(t)$$

$$\frac{dF_2(t)}{dt} = -L_{21}F_1(t) + (L_{02} + L_{12})F_2(t)$$

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In order to simplify the solution of this set of equations, we will make some assumption about the system we are trying to represent:

a) $F_1(0)=100$ %, and $F_2(0)=0$ % (all tracer in container 1 at t=0)

b) $(L_{01} + L_{21}) = L_{11}$, and $(L_{02} + L_{12}) = L_{22}$

c) No losses from container 1 to environment, i.e. $L_{01} = 0$

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This reduces eq. 1 and eq. 2 to the following:

$$\frac{dF_1(t)}{dt} = -L_{11}F_1(t) + L_{12}F_2(t)$$

$$\frac{dF_2(t)}{dt} = -L_{21}F_1(t) + L_{22}F_2(t)$$

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$m=(1/2)*[-(L_{11}+L_{22}) \pm \{(L_{11}+L_{22})^2-4(L_{11}L_{22}-L_{12}L_{21})\}^{1/2}]$

General solution:

$F_1(t) = a_1\exp(m_1t) + b_1\exp(m_2t)$
$F_2(t) = a_2\exp(m_1t) + b_2\exp(m_2t)$

Specific solution:

Apply initial conditions and solve.

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Kinetic Models - Calculations

Example: A radiopharmaceutical labeled with ^{99m}Tc has a 20% uptake in the liver and a biological half-time of 12 hours. What will be the number of disintegrations from an administration of 20 MBq?

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Kinetic Models - Calculations

$$\frac{1}{T_e} = \frac{1}{T_f} + \frac{1}{T_b} \qquad T_e = \frac{T_f \times T_b}{T_f + T_b}$$

$$T_e = \frac{6\,h \times 12\,h}{6\,h + 12\,h} = 4h$$

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Kinetic Models - Calculations

$$N = 1.443 \times A_0 \times T_{1/2} = 1.443 \times 0.2 \times 20\ MBq \times 4\ h = 23\ MBq - h$$

$$(23\ MBq - h)\left(\frac{10^6\ Bq}{MBq}\right)\left(\frac{1\ dis}{Bq - s}\right)\left(\frac{3600\ s}{h}\right) = 8.3x10^{10}\ dis$$

Rinse, lather, repeat…..repeat……repeat

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Radiocontaminants in a radiopharmaceutical product

- ^{201}Tl chloride has been used in myocardial imaging.
- The biokinetic model (ICRP 53) suggests uptake and clearance functions for 17 separate organs.
- Formulations of ^{201}Tl may also contain ^{200}Tl and ^{202}Tl as low level radioactive contaminants.

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Radiocontaminants in a radiopharmaceutical product

	Dose (mGy/MBq)		
Target Organ	Tl-201	Tl-200	Tl-202
LLI Wall	2.24E-01	7.69E-02	3.10E-01
Small Intestine	3.05E-01	1.03E-01	4.13E-01
ULI Wall	1.86E-01	6.26E-02	2.52E-01
Heart Wall	1.83E-01	6.32E-02	2.42E-01
Kidneys	3.07E-01	1.03E-01	4.36E-01
Liver	4.31E-02	1.45E-02	6.09E-02
Ovaries	1.72E-02	5.28E-03	3.02E-02
Red Marrow	1.72E-02	5.28E-03	3.02E-02
Spleen	9.98E-02	3.22E-02	1.75E-01
Testes	1.57E-01	5.15E-02	4.55E-01
Thyroid	4.74E-01	1.55E-01	7.05E-01
Urin Bladder Wall	1.36E-02	4.25E-03	2.25E-02
Total Body	2.42E-02	7.65E-03	4.02E-02

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If we consider a ^{201}Tl product that is assumed to be 97% ^{201}Tl, 2% ^{200}Tl and 1% ^{202}Tl, we need to add the dose contributions from the primary product and the two contaminants. Taking 0.97 times the value in the first column, 0.02 times the value in the second column and 0.01 times the value in the third column, we obtain the estimates for the product with contaminants:

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Target Organ	Dose (mGy/MBq)
LLI Wall	2.22E-01
Small Intestine	3.02E-01
ULI Wall	1.84E-01
Heart Wall	1.81E-01
Kidneys	3.04E-01
Liver	4.27E-02
Ovaries	1.71E-02
Red Marrow	1.71E-02
Spleen	9.92E-02
Testes	1.58E-01
Thyroid	4.70E-01
Urin Bladder Wall	1.35E-02
Total Body	2.40E-02

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Urinary Excretion

- One of the more difficult organs to model from a kinetic standpoint is the urinary bladder.
- Material in the blood is being constantly passed through the kidneys, where 2 processes, glomerular filtration and tubular excretion, extract certain substances and concentrate them in a fluid that passes into the urinary bladder, which is a hollow organ.
- Periodically, when a significant amount of fluid has accumulated, the bladder is emptied, and the process of filling begins again.

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Urinary Excretion

- Material leaving the body is most often governed by first order processes, which mean that the *retention* (in the body) can be expressed as a function such as A*exp(-λ t).
- Therefore, the time-activity curve for the bladder takes the form of A*(1 - exp(-λ t)).
- BUT the curve is periodically interrupted by voiding and goes to zero (or nearly zero) and then begins to accumulate again:

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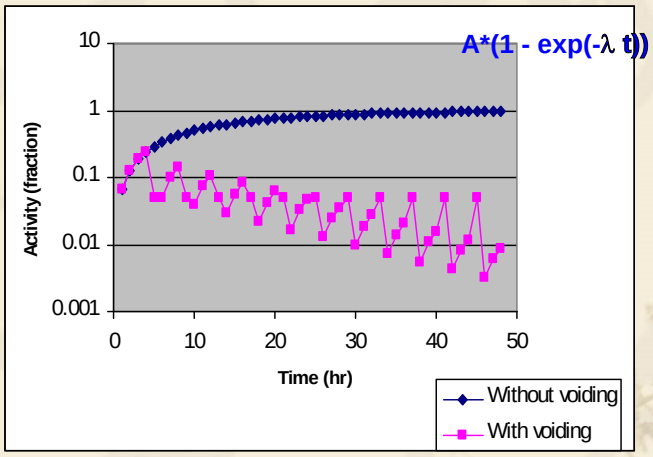

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Urinary Excretion

- It is not possible to accumulate enough data to characterize the real curve (with voiding); what is needed is a characterization of the values A and λ (in real situations there may be more than one term in the equation, but for now, let's just consider one).
- In a particularly ingenious derivation, Walt Snyder and colleagues (Cloutier et al. 1973a) showed that the number of disintegrations occurring in the bladder could be given in such cases by a single equation:

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Urinary Excretion

$$N = A_0 \sum_i f_i \left[\frac{1 - e^{-\lambda_i T}}{\lambda_i} - \frac{1 - e^{-(\lambda_i + \lambda_p)T}}{\lambda_i + \lambda_p} \right] \left[\frac{1}{1 - e^{-(\lambda_i + \lambda_p)T}} \right]$$

- Here, A_0 is the initial activity entering the body, λ_p is the physical decay constant of the radionuclide, λ_i is the biological removal constant for the fraction of activity f_i leaving the body via the urinary pathway, and T is the bladder voiding interval, assumed to be constant.

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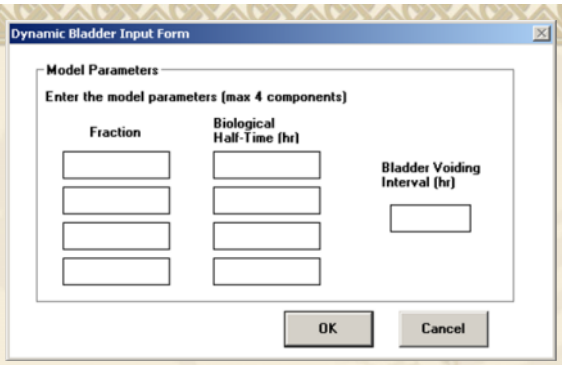
Urinary Excretion

- If we have all the activity in the body passing out through the urinary pathway with a 1 hour half-time, for example, our f would be 1.0 and λ would be 0.693/1 = 0.693 hr^{-1}.
- Let's say we have 40% passing out through the GI tract, and 60% through the urinary pathway, with half of the urinary clearance having a half-time of 1 hour and half with a half-time of 10 hours.
- Then f_1 would be 0.3 and λ_{b1} would be 0.693 hr^{-1}, and f_2 would also be 0.3 and λ_{b2} would be 0.0693 hr^{-1}.

65



$$N_{TB} = \int_0^{\infty} A_{TB_i} e^{-a_{TB_i} t}\, dt = \frac{A_{TB_i}}{a_{TB_i}} = 1.443 \times A_{TB_i} \times T_{1/2_{TB_i}}$$

$$N_{RB} = N_{TB} - \sum N_{organs}$$

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Gastrointestinal (GI) Excretion

- The dosimetric model for the gastrointestinal tract (GI tract) given in ICRP 30 (ICRP 1979) is a very simple, straight-through, four-compartment model.
- The four sections are stomach, small intestine, upper large intestine, and lower large intestine, sometimes abbreviated ST, SI, ULI, and LLI, respectively.
- The sections of the GI tract are treated as separate target tissues according to the recommendations in the ICRP dosimetric system

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Stomach
λ_{ST}
Mean time = 1 hr
λ_b
Small Intestine
λ_{SI}
Mean time = 4 hr
Upper Large Intestine (ULI)
λ_{ULI}
Mean time = 13 hr
Lower Large Intestine (LLI)
λ_{LLI}
Mean time = 24 hr
Feces
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Activity input to the:
Stomach
Small Intestine
Fraction entering:
Fractional SI absorption:
OK
Cancel
69

America's Best Hospitals: the 2009–10 Honor Roll

They're the best of the best—the 0.4 percent of all hospitals with high scores in 6 or more specialties

By Avery Comarow
Posted July 15, 2009

America's Best Hospitals, an annual ranking of the country's elite medical centers, is a tool for patients who need medical sophistication most facilities cannot offer. Unlike other rankings and ratings that grade hospitals on how well they execute routine procedures like outpatient hernia repair or manage common conditions like low-grade heart failure, the *U.S. News* approach looks at how well a hospital handles complex and demanding situations—replacing an 85-year-old man's heart valve, diagnosing and treating a spinal tumor, and dealing with inflammatory bowel disease, to name three examples. High-stakes medicine.

Click to view video.

This year, the 20th for Best Hospitals, institutions are ranked in 16 specialties, from cancer and heart disease to respiratory disorders and urology. A total of 4,861 hospitals were considered; 174, or less than 0.4 percent of the total, were ranked in even one of the 16 specialties.

In 12 of the 16 specialties, those in which quality of care can spell life or death, hospitals were scored on reputation, death rate, patient safety, and care-related factors such as nursing and patient services; the 50 highest scorers were ranked. Scores and complete data for unranked hospitals are available as well. In the other four specialties—ophthalmology, psychiatry, rehabilitation, and rheumatology—hospitals were ranked on reputation alone, because so few patients die that mortality data don't mean much.

Here are a few of the details: Reputation, which counted as 32.5 percent of the score, was based on three years of specialist surveys—a total of almost 10,000 physicians were asked to name five hospitals they consider among the best in their specialty for difficult cases, without taking into account cost or location. A mortality index, also 32.5 percent of the score, indicates a hospital's ability to keep patients with serious problems alive. Patient safety, new this year, made up 5 percent of the score; it indicates how well a hospital minimizes harm to patients. And a group of other care-related factors, such as nurse staffing and available technology, accounted for the remaining 30 percent.

Of the 174 hospitals that are ranked in one or more specialties, 21 qualified for the Honor Roll by earning high scores in at least six specialties. This demonstrates unusual breadth of excellence. Johns Hopkins Hospital tops the list, as it has every year from 1991 on. (The Mayo Clinic was No. 1 in 1990, Best Hospitals' first year.)

Hospitals are listed by total points. A hospital got 2 points if ranked at or close to the top in a specialty and 1 point if ranked slightly lower.

Rank	Hospital	Points	Specialties
1	Johns Hopkins Hospital, Baltimore	30	15
2	Mayo Clinic, Rochester, Minn.	28	15
3	Ronald Reagan UCLA Medical Center, Los Angeles	26	15
4	Cleveland Clinic	26	13
5	Massachusetts General Hospital, Boston	25	13
6	New York-Presbyterian University Hospital of Columbia and Cornell	24	13
7	University of California, San Francisco Medical Center	21	11
8	Hospital of the University of Pennsylvania, Philadelphia	19	12

9	Barnes-Jewish Hospital/Washington University, St. Louis	17	12
10	Brigham and Women's Hospital, Boston	17	10
10	Duke University Medical Center, Durham, N.C.	17	10
12	University of Washington Medical Center, Seattle	16	8
13	UPMC-University of Pittsburgh Medical Center	13	8
14	University of Michigan Hospitals and Health Centers, Ann Arbor	12	8
15	Stanford Hospital and Clinics, Stanford, Calif.	11	7
16	Vanderbilt University Medical Center, Nashville	11	6
17	NYU Medical Center, New York	10	7
17	Yale-New Haven Hospital, New Haven, Conn.	10	7
19	Mount Sinai Medical Center, New York	9	7
20	Methodist Hospital, Houston	8	7
21	Ohio State University Hospital, Columbus	7	6