Modeling of decorporation Therapy

The importance of USTUR data

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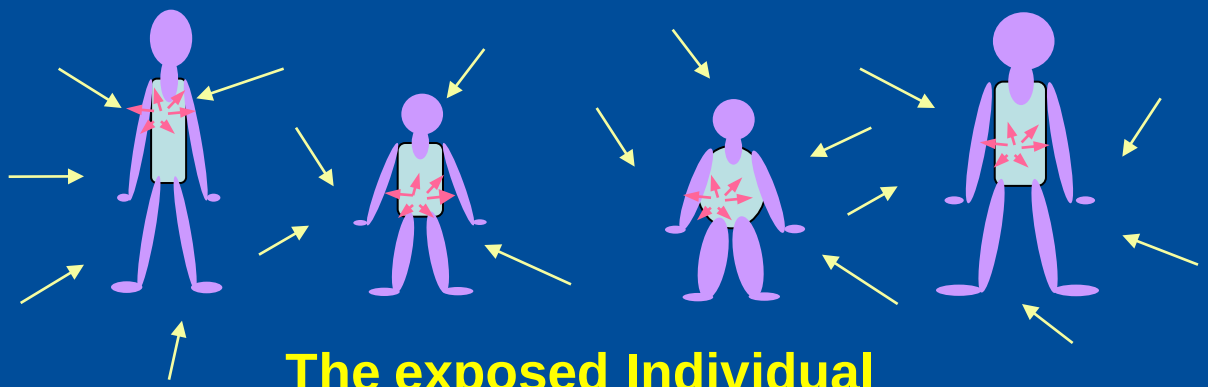
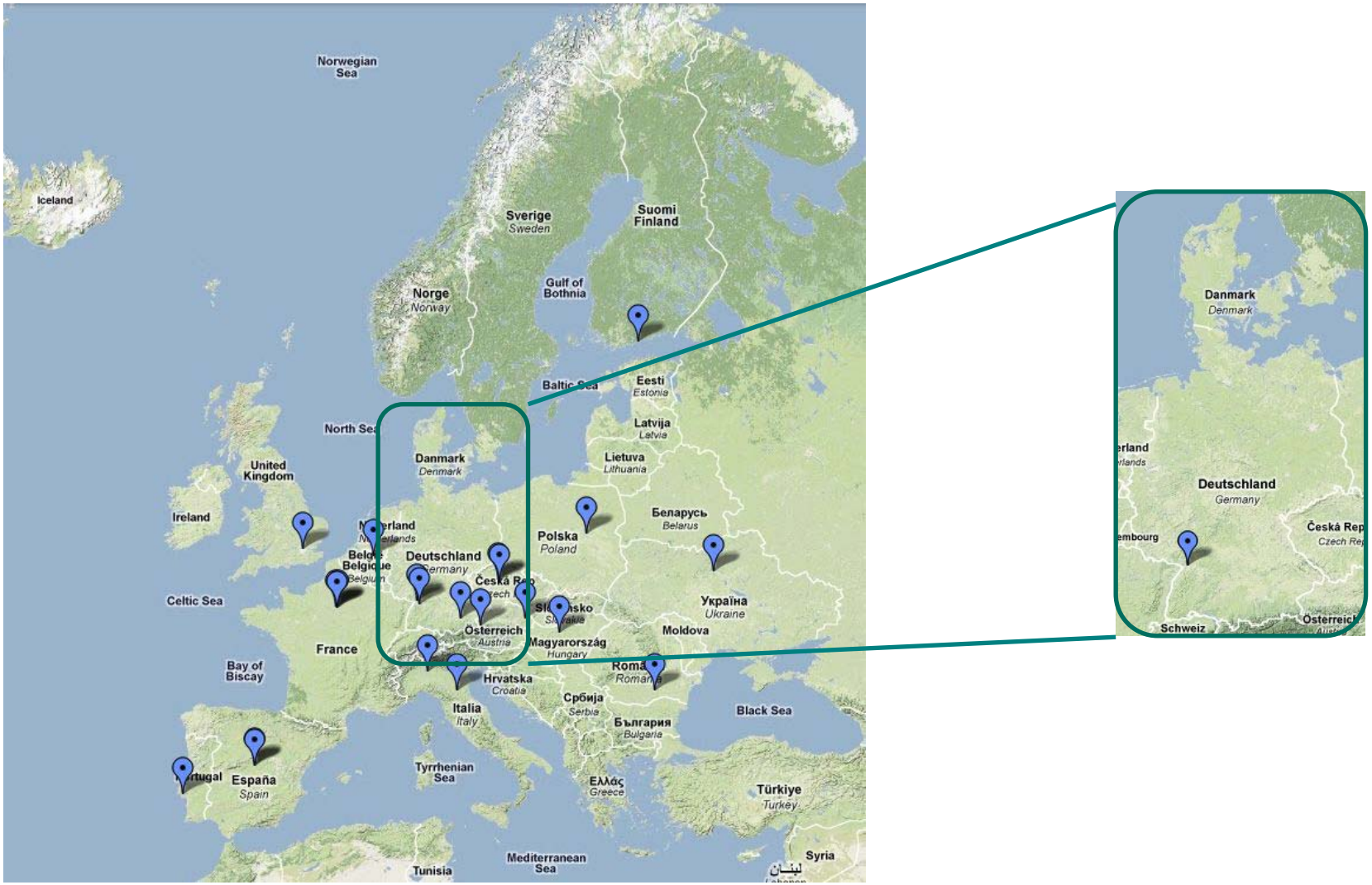


Outline

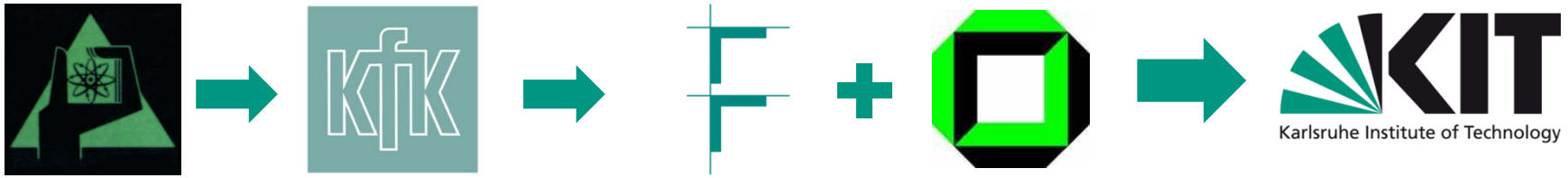
- „Commercial Break“
  - KIT and EURADOS
- Decorporation Therapy with DTPA
- The CONRAD/EURADOS Approach to modeling DTPA Therapy
  - Basic Model
- Using USTUR data for enhancing the EURADOS model

EURADOS and KIT



KIT – Karlsruhe Institute of Technology

- Founded in 2010 as merger of the former Research Centre Karlsruhe and the University of Karlsruhe



  - Mission of a research institution of the Helmholtz Association with programoriented provident research
  - Mission of a state university with research and teaching

Employees
8,500
Students
19,700
364
Professors
650
Annual Budget in Million Euros

EURADOS Working Group 7

- EUROpean RADiation DOSimetry Group
  - is a network of >50 institutions and >200 scientists from the European Union, Switzerland, Eastern and Central Europe
  - serves the promotion of research and development and European cooperation in the field of the dosimetry of ionizing radiation
  - http://www.eurados.org

- EURADOS Working Group 7 – “Internal Dosimetry”
  - Coordinator: M.A. Lopez (CIEMAT, Madrid, Spain)
  - Currently 5 Taskgroups
    - Revision of IDEAS Guidelines
    - Biokinetic Models
    - Modeling of Decorporation Therapy
    - Monte Carlo Methods for in-vivo Monitoring
    - Uncertainties in internal Dosimetry

EURADOS WG7 – Internal Dosimetry Network

- ACJ & Associates (U.S.A.)
- AEKI (Hungary)
- ARN (Argentina)
- BfS (Germany)
- CEA (France)
- CIEMAT (Spain)
- EDF (France)
- ENEA (Italy)
- KIT, Karlsruhe (Germany)
- Helmholtz Zentrum München (Germany)
- HML (Canada)
- HPA (UK)
- IAEA
- IDEA-System (Germany)
- IRSN (France)
- Institute of Atomic Energy (Poland)
- ITN (Portugal)
- Los Alamos National Lab (U.S.A.)
- NIPNE (Romania)
- NRPI (Czech Rep.)
- RPI-Kiev (Ukraine)
- SCK-CEN (Belgium)
- STUK (Finland)
- TECNATOM (Spain)
- Univ. Milan (Italy)
- Univ. Prague (Czech Rep)
- Univ. Salzbourg (Austria)
- USTUR/WSU (U.S.A.)

28 Institutes

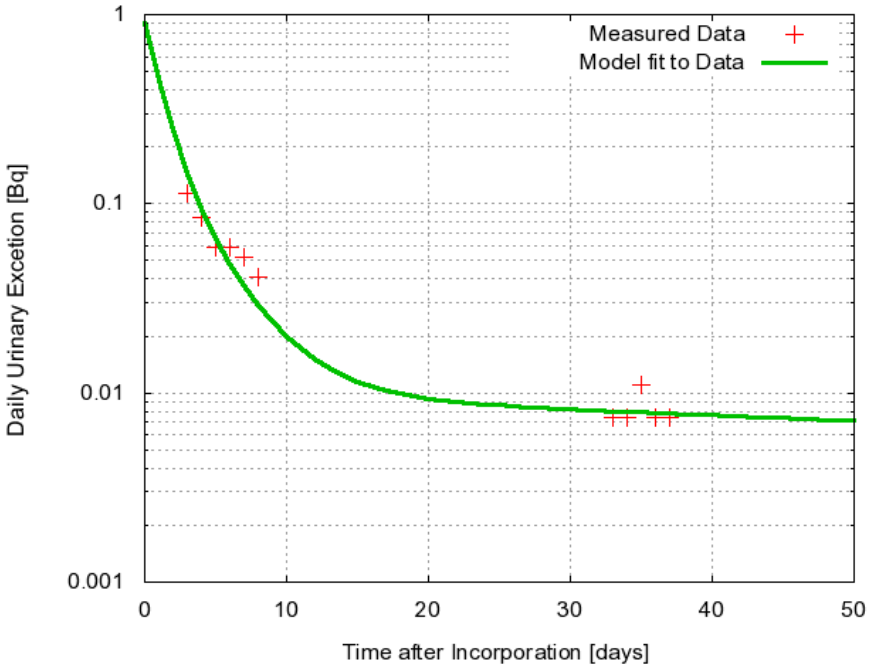
17 Countries

3 Continents

End of „Commercial Break“

Decorporation Therapy with DTPA

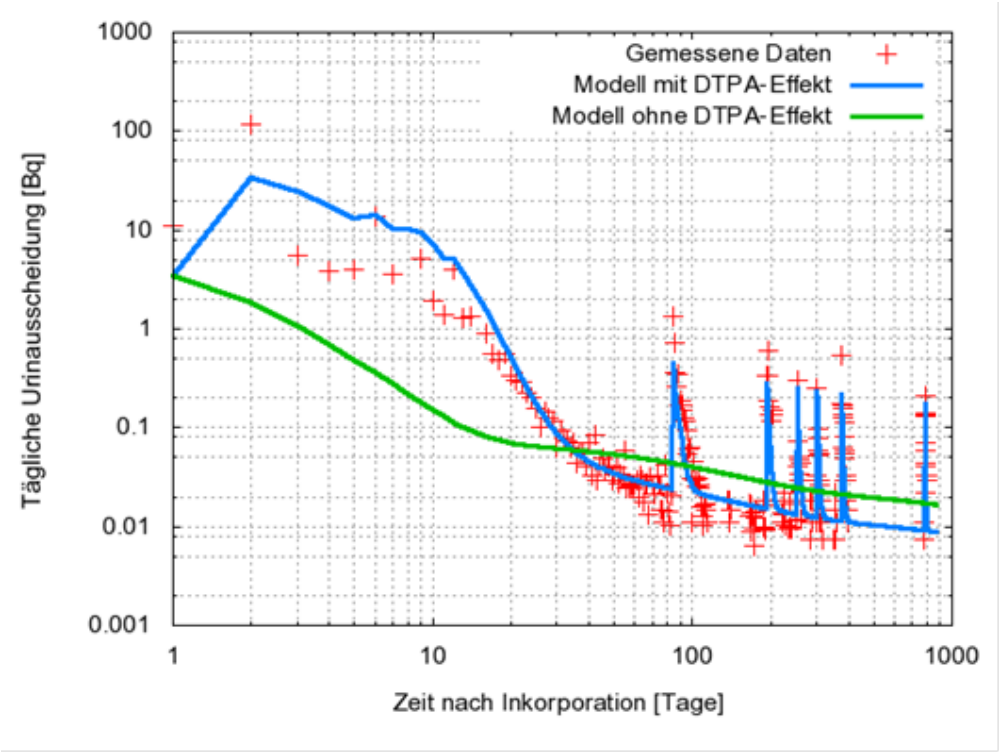
- Dose assessment after incorporation of Pu and Transuranium elements requires
  - biokinetic models of urinary excretion for estimation of intake and number of decays
    - „official“ ICRP Models and research models e.g. Leggett 2005 are available



  - Dosimetric models to calculate absorption of energy after decays of radionuclides

Decorporation Therapy with DTPA

- Excretion of Pu and Transuranium elements can be enhanced by i.v. administration of salts of DTPA (**D**i-ethlyene-**T**riamine-**P**enta-**A**cid)
  - enhanced urinary excretion after DTPA-injection (up to 100 times baseline)
    - effect can be observed for several days: Ceases exponentially with two half-lifes

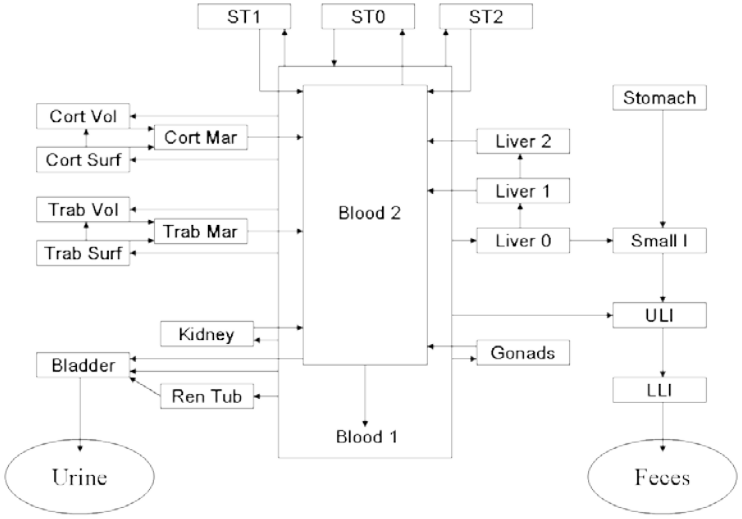


Decorporation Therapy with DTPA

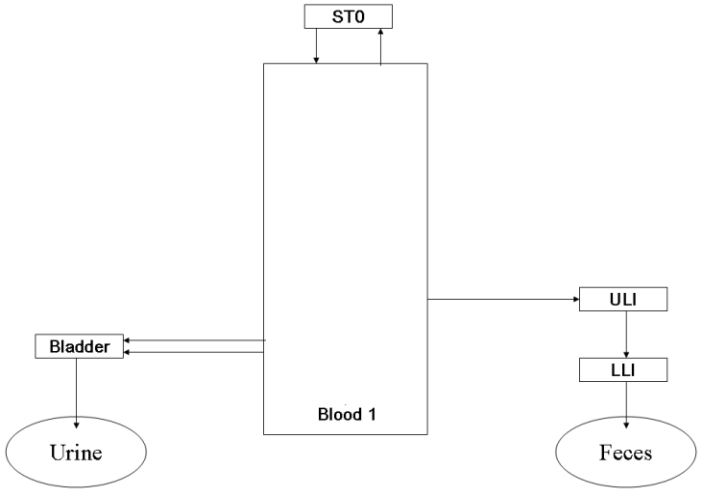
- Dosimetric benefit of DTPA-therapy?
  - „What‘s left the body can‘t deliver dose inside.“
  - Assessment of dose is not possible using reference models/techniques
    - Reference models describe undisturbed biokinetics
  - Complication
    - Best dose assessment → late therapy (many undisturbed data before)
    - Best therapeutic effect → early therapy (no undisturbed data available)
  - Need to develop a generic model of decorporation therapy
    - Development started in CONRAD project (EC funded: 2005 -2008)
    - Work now continued in EURADOS WG7

The CONRAD/EURADOS model

- Idea: Combine models of undisturbed biokinetics of Pu and DTPA
  - Plutonium: Model for undisturbed biokinetics of Pu (Leggett et al. 2005)
  - Injected DTPA: Model for ^{14}C-DTPA biokinetics (Stather et al. 1983)
  - Chelated Pu: Model for ^{14}C-DTPA biokinetics (Stather et al. 1983)
    - Assumption: negligible dependence of DTPA kinetics on metal ion
    - Reduces number of parameters



Leggett et al: Radiation Research 164:111-122: 2005



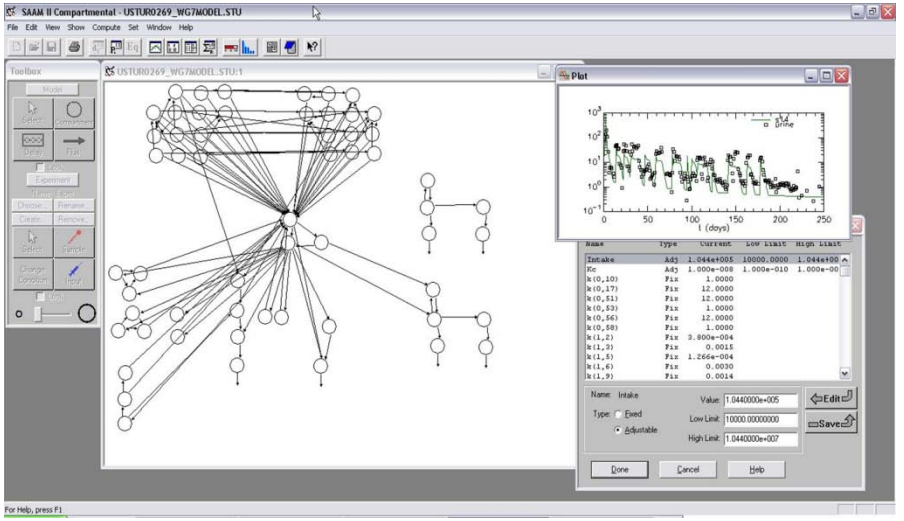
After: Stather et al: Health Physics 44:45-52: 1983

The CONRAD/EURADOS model

- Equations
  - Three coupled equation systems
    - X: injected DTPA
    - Y: Plutonium
    - Z: Pu-DTPA complexes
  - Excretion
    - Sums of systems X + Z
  - New Parameter KR

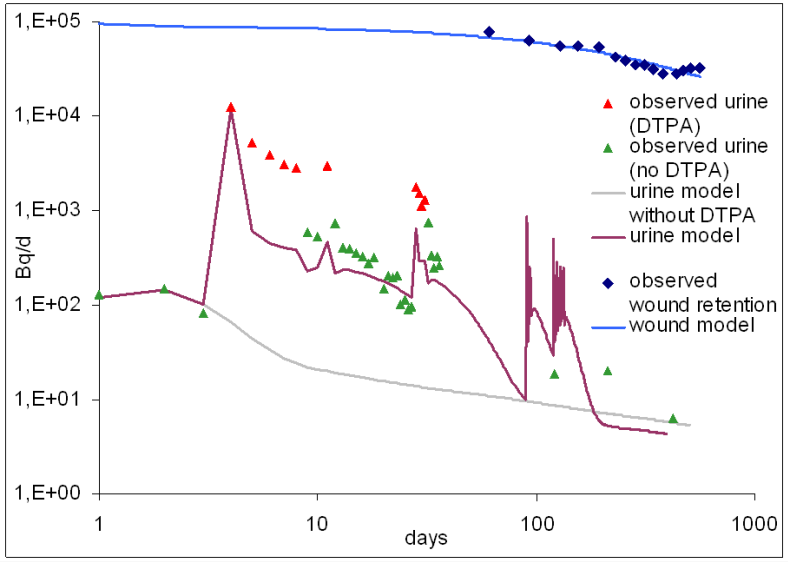
biokinetics	complexation
$\frac{dx_i}{dt} = -\sum_{j=1}^{n} k_{ij} x_i + \sum_{j=1}^{n} k_{ji} x_j$	$- KR \cdot f(x_i, y_i)$
$\frac{dy_i}{dt} = -\sum_{j=1}^{n} k_{ij} y_i + \sum_{j=1}^{n} k_{ji} y_j$	$- KR \cdot f(x_i, y_i)$
$\frac{dz_i}{dt} = -\sum_{j=1}^{n} k_{ij} z_i + \sum_{j=1}^{n} k_{ji} z_j$	$+ KR \cdot f(x_i, y_i)$

- Numerics
  - Cheating SAAM-II software
    - Not intended for 2nd order kinetics
  - Slow integration
  - Handling several orders of magnitude
  - „Hundred ways to crash SAMM II“



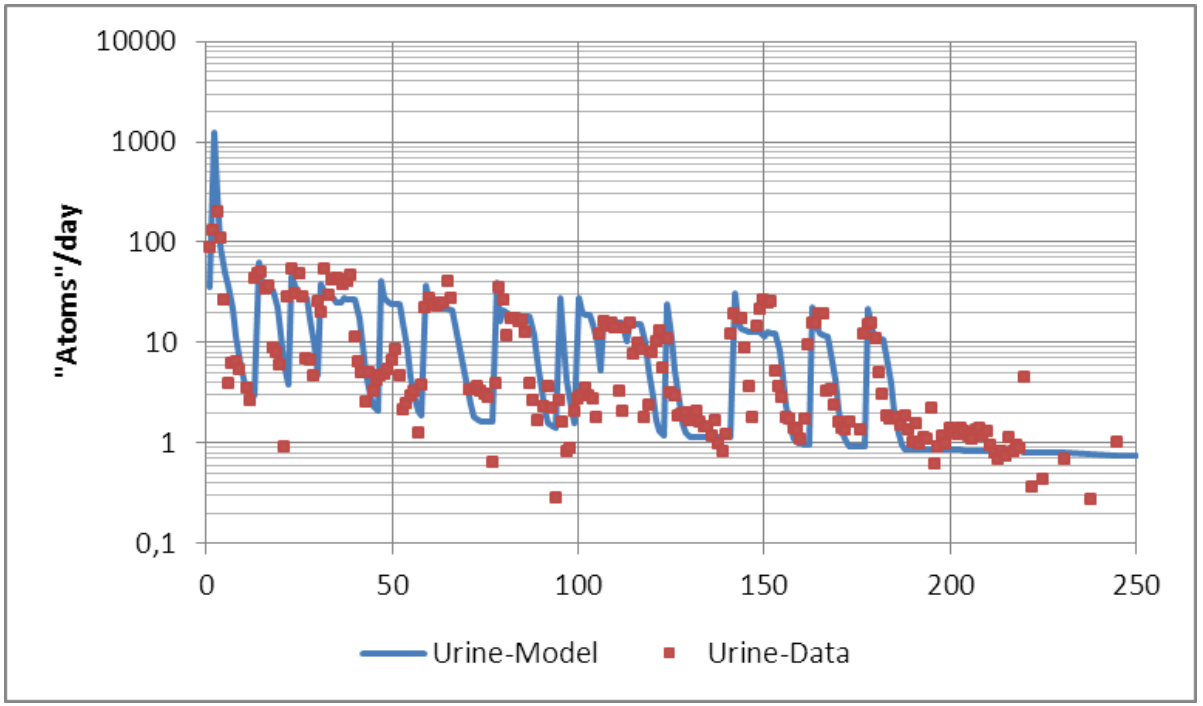
The CONRAD/EURADOS model

- Studies with the models
  - Theoretical scenarios
  - Cases taken from IDEA- and USTUR-Databases
- Problems encountered
  - Unable to predict lasting effect of DTPA
    - all Pu in compartment is removed „immediately after DTPA is available“ (DTPA: Pu > 1E6)
  - Unable to describe multiple chelations
    - First injections clears all Pu (undisturbed recycling is not fast enough)



USTUR Case 0269

- 1956: Inhalation of ~58 kBq Pu (Nitrate), massively chelated
  - Lots of data, including tissue content at death (38y after intake)
  - First Treatments with EDTA (before DTPA was available)

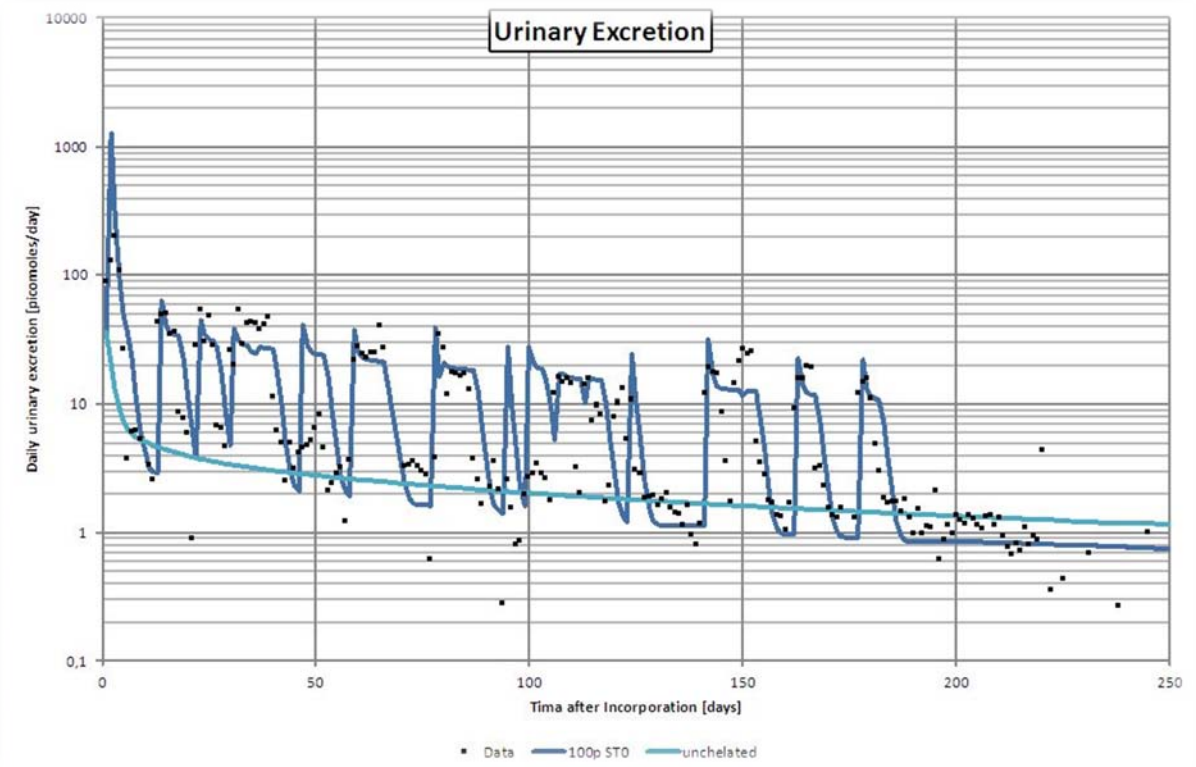


Urinary Excretion of USTUR Case 0269: Original CONRAD model (EDTA-therapies)

Case Description: James AC et al, Radiation Protection Dosimetry, 127, 449-445 (2007).

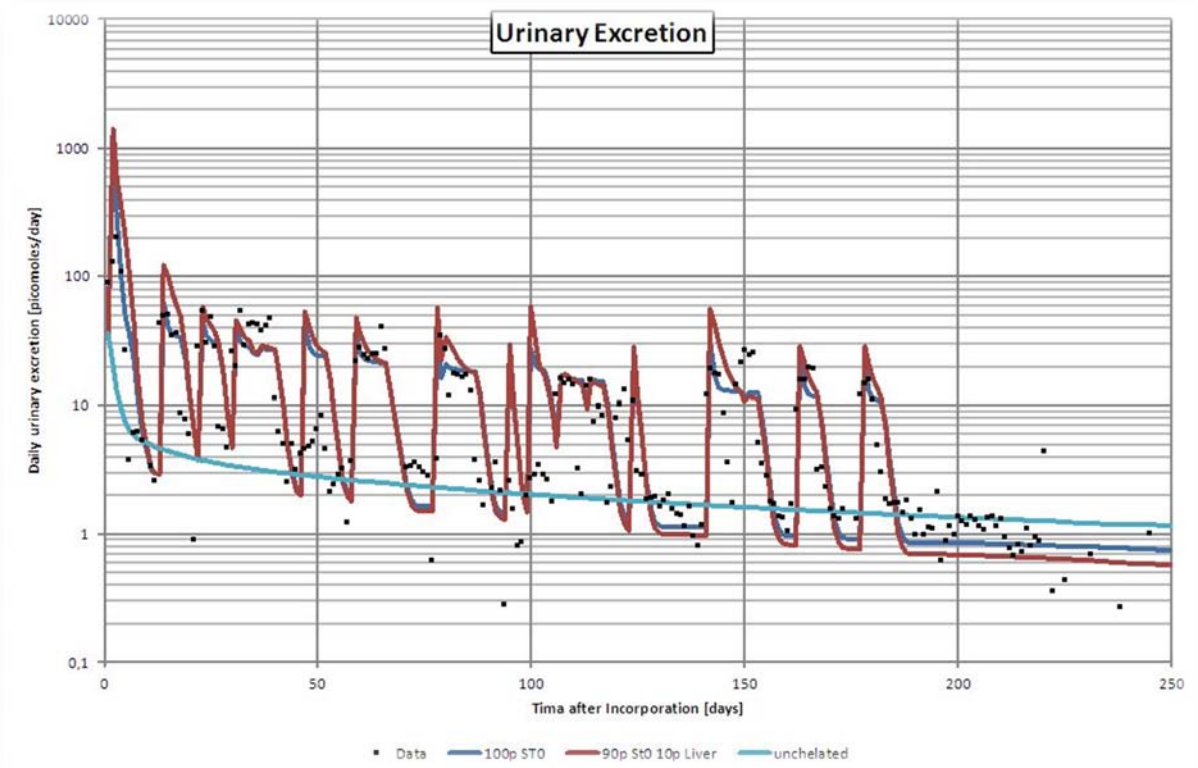
The CONRAD/EURADOS model

- Study with USTUR case 0269 data
  - Original model: Chelation only in ST0 compartiment (= extracellular fluids)



The CONRAD/EURADOS model

- Study with USTUR case 0269 data
  - Original model: Chelation only in ST0 compartiment (= extracellular fluids)
  - Modification 1: Chelation 90% in ST0 and 10% in liver



The CONRAD/EURADOS model

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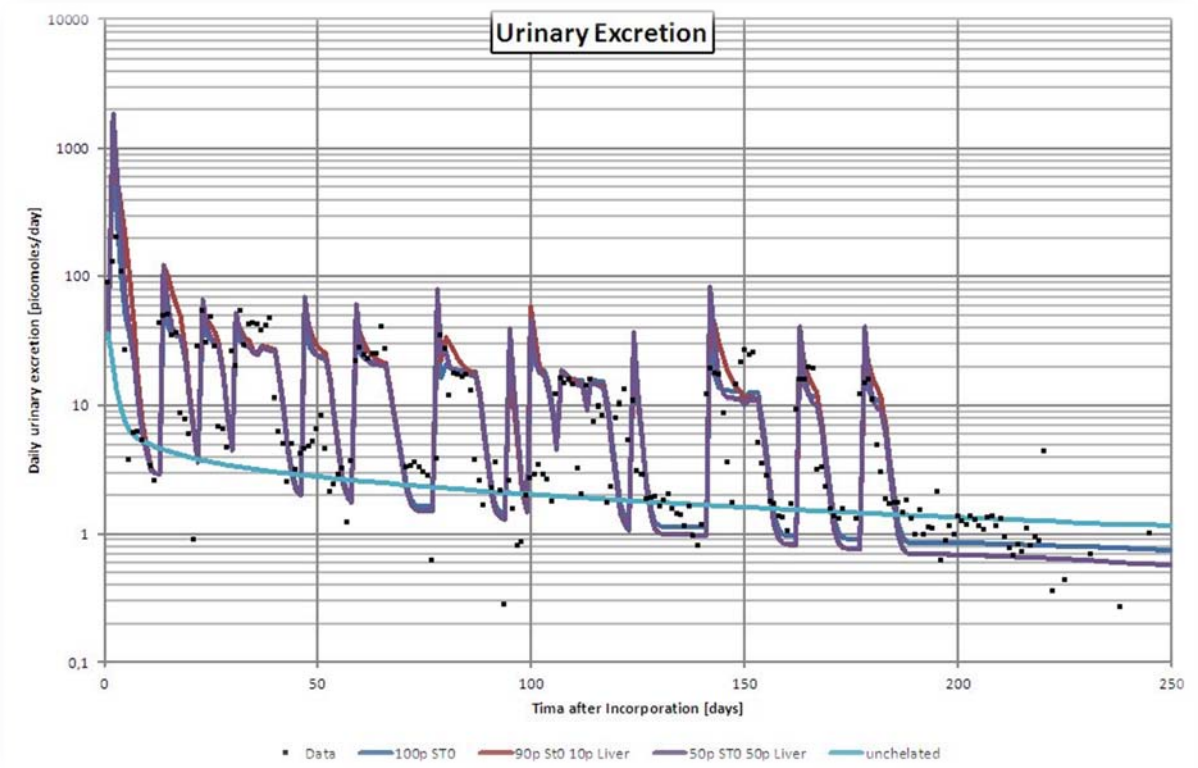
  - Modification 1: Chelation 90% in ST0 and 10% in liver
  - Modification 2: Chelation 50% in ST0 and 50% in liver



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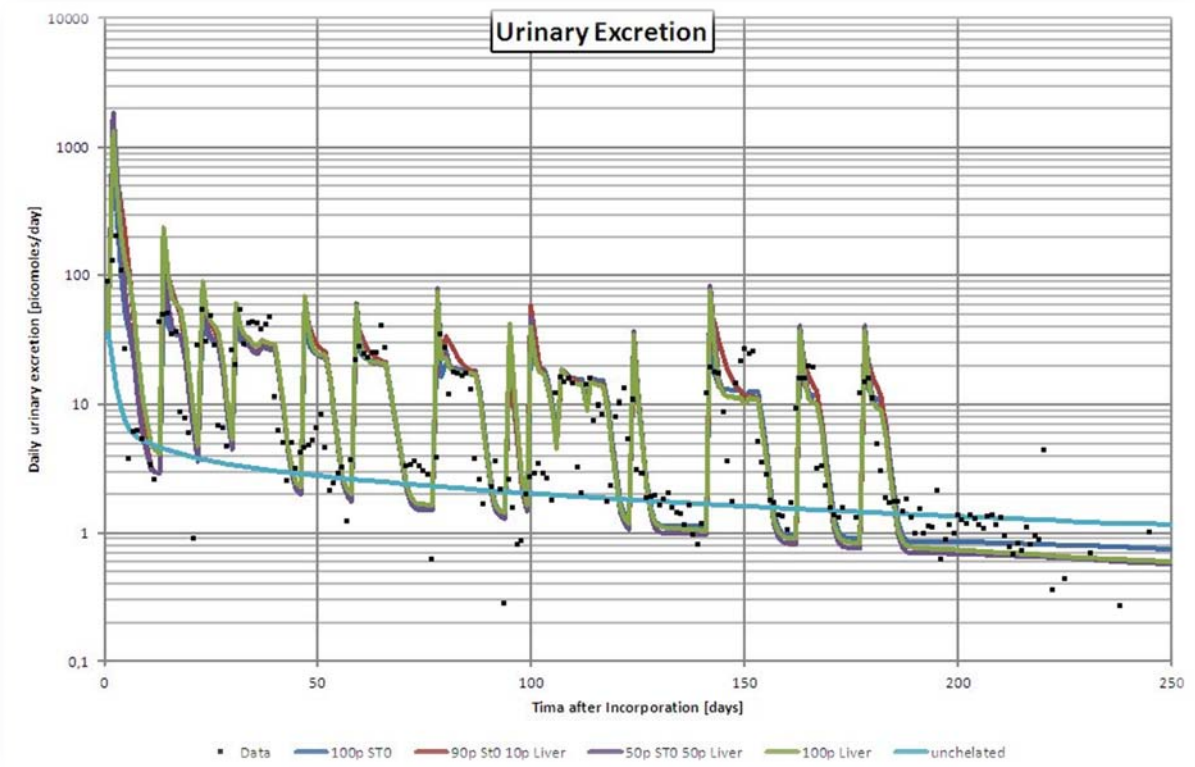
  - Modification 3: Chelation only in liver



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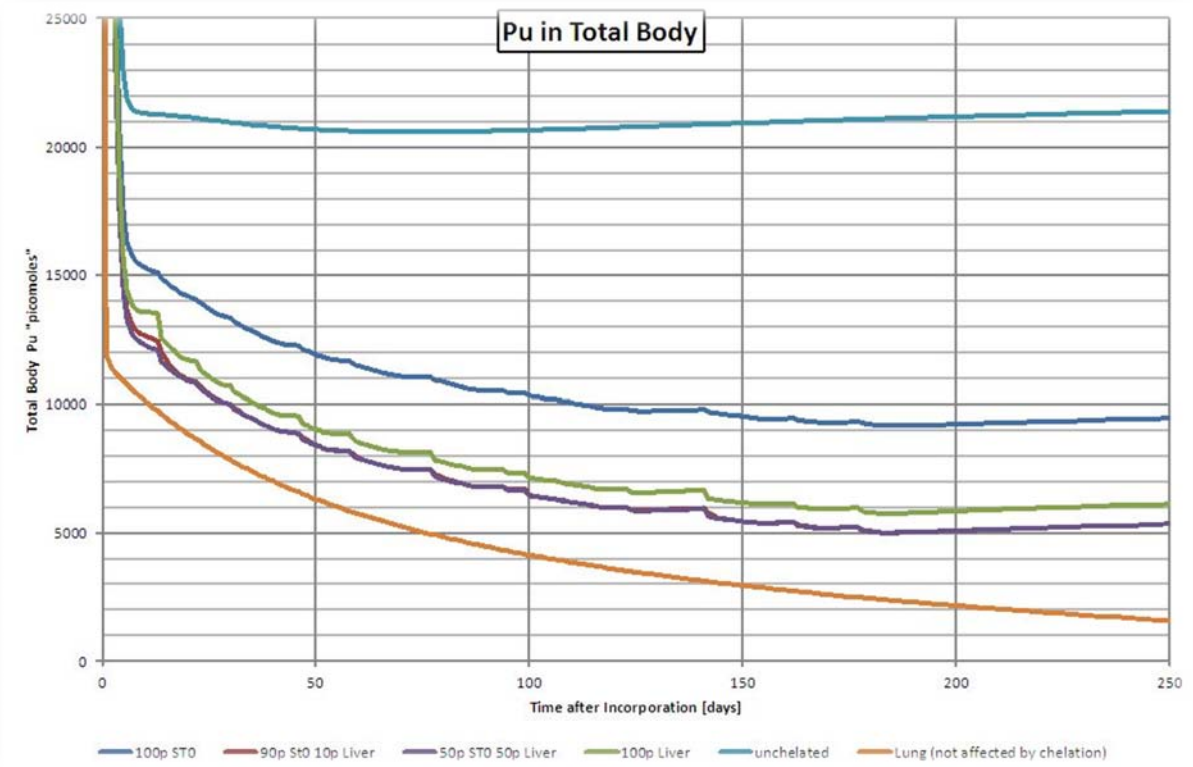


Modeling of DTPA-decorporation therapy

- We can‘t see where the actinide came from by looking only at urinary excretion
  - Further information required for modeling
- USTUR is a goldmine for biokinetic modeling with extensive sets of data
  - Health Physics data (urinary and fecal excretion) data
  - Autopsy data
    - gives the endpoint of distribution inside body
  - Sometimes additional information available
    - In-vivo bioassay
    - Workplace data
- USTUR is an unfortunately underappreciated resource of data for
  - Biokinetic modeling of uranium and transuranium elements
  - Epidemiological/Radiobiological studies of health effects of transuranium elements
  - Development and Testing of analytical methods (radiochemistry)
  - Statistical analysis for estimation of uncertainties in dosimetry

KIT sabbatical - „Data mining at USTUR“

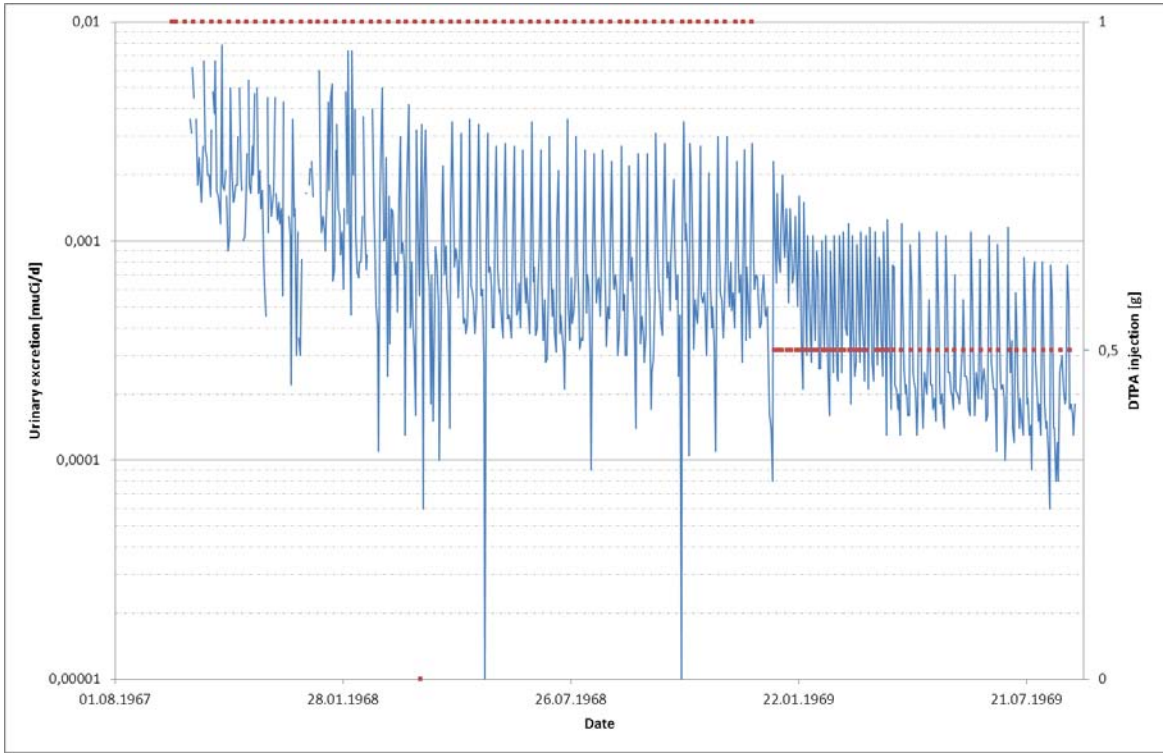
- Aim: Further development of EURADOS-model by using USTUR case data

- Focus on Am-241 incorporation: USTUR Case 0846
  - Chronic Inhalation of Am-241 (estimated body burden 67 kBq)
  - Person died 41 years after end of intake
  - massive Chelation therapy (seven years with weekly injections of 1g DTPA)
  - Several publications with case report and studies in Health Physics Journal
  - Studies for in-vivo measurement with left leg
    - ISU PhD-student M. Kahlaf

- Data set available
  - Complete set of data for urine measurements
  - Some In-vivo Measurements and Fecal data
  - Post mortem In-vivo Measurements available (PNNL)
  - Autopsy Data will be available (in 2011/12)

KIT sabbatical - Case 0846

- Digitizing of Data from Publications in Excel-Spreadsheet
- Analysis of hardcopy files and extraction of data



Urinary Excretion of USTUR Case 0846: Data for first two years

KIT sabbatial - Case 0846

- Digitizing of Data from Publications
- Analysis of hardcopy files and extraction of data
- Consolidation of data and generation of final set of data
- Implementation of EURADOS model in SAAM II and Model Maker 4
  - First time for Am-241 biokinetics
- Fitting of data and refining CONRAD model
- Publication(s) in Journals

KIT sabbatial - Case 0269

- Using revised dataset from USTUR database
- Implementation of EURADOS model in SAAM II and Model Maker 4
- Studies with different modification of the models
- Fitting of data
- Comparison with analysis of James et al. 2007
- Publication(s) in Journals

KIT sabbatical - Outlook

- Collaboration (KIT – USTUR - EURADOS WG 7) shall be continued
- Use further USTUR case data for statistical analysis of DTPA-cases
  - Apply Revised Model
  - Derive Parameters for DTPA-model for available Cases
  - Generalize Model
  - Generate „generic“ model of DTPA therapy

- Biokinetic Modeling of non-chelated Cases
- Bachelor/Master/PhD thesis using USTUR data
- Application of analytical methods for actinide chemistry available at KIT

Karlsruhe Institute of Technology

European Radiation Dosimetry Group

Thank you for your attention