The NIAID Radiation Nuclear Countermeasures and Biodosimetry Development Program: An Overview

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Disclaimer

- This material is presented from my own perspective, and should not be taken as representing the viewpoint of the Department, NIH, or NIAID.
NIAID-RNCP Architecture: Who are we?

National Institutes of Allergy and Infectious Diseases
Office of the Director

- Division of Intramural Research
- Division of AIDS
- Division of Microbiology and Infectious Diseases
- Division of Extramural Activities
- Division of Allergy, Immunology and Transplantation

- Office of Regulatory Affairs
- Office of Program Planning, Operations, and Scientific Information
- Clinical Research Operations Program
- Radiation and Nuclear Countermeasures Program
- Division of Clinical Research
- Vaccine Research Center
In 2004, NIAID was directed by HHS to foster a research program to accelerate development of radiation/nuclear medical countermeasures (MCMs) for the Strategic National Stockpile.

Mission:

- Support early to mid-stage research to develop radiation/nuclear MCMs and biodosimetry devices
- Provide funding opportunities:
  - Grants, collaborative agreements, contracts, inter- and intra-agency agreements
Sources of Environmental Radiation Contamination

- Natural sources:
  - Cosmic Radiation (Uranium, Thorium)
  - Terrestrial Radiation (Uranium, Actinium, Thorium series)
  - Internal Radiation (Soil, water, vegetation-Uranium, thorium, Radon)

- Man-made sources:
  - Radioactive material in medicine (Diagnostics, therapeutics, research)
  - Industry
  - Nuclear industry
  - Nuclear warfare
Background radiation

Radiation is everywhere

We live in a sea of radiation...
Man-made radiation
Fallout pattern after a radiological event

Figure 14: Contour heat damage and maximum, median, and minimum ranges for detonations of 0.1 T, 1.0 T, and 10 T.

Figure 15: Simulation of multiple-proposed fallout zones contingent with time for a 10 T detonation.

View from the South, 15 minutes after detonation

Fallout Clouds Drop Contamination

Contamination remains on the ground giving off radiation
Medical intervention is a small aspect of the enormous problem.....
Important aspects of fallout

- Fallout decay rapidly - Releasees more than half its energy in the first hour
- Primary hazard is exposure to deeply penetrating particulate radiation
- Fallout is visible - such as salt or sand
- Fallout is not a significant inhalation hazard
Primary consideration for fallouts: human safety

A protection factor of just 10 or higher is considered adequate protection against fallout radiation. For simple, wood frame houses, just going into a basement is enough to offer adequate protection. For those in large office or apartment buildings, going into the center of the building or deep underground offers very high levels of protection against radiation.
 Fallout results in exposure over long distance…
 However fallout comprises of a complex mixture of radioactive isotopes with different half lives

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Half-life</th>
<th>Nuclide</th>
<th>Half-life</th>
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</thead>
<tbody>
<tr>
<td>$^{55}$Fe$^a$</td>
<td>2.7 a</td>
<td>$^{127}$Sb</td>
<td>3.9 d</td>
</tr>
<tr>
<td>$^{64}$Cu$^a$</td>
<td>13 h</td>
<td>$^{129}$Te</td>
<td>70 min</td>
</tr>
<tr>
<td>$^{77}$As</td>
<td>39 h</td>
<td>$^{129}$Sb</td>
<td>4.4 h</td>
</tr>
<tr>
<td>$^{83}$Br</td>
<td>2.4 h</td>
<td>$^{131}$I</td>
<td>30 h</td>
</tr>
<tr>
<td>$^{88}$Rb</td>
<td>18 min</td>
<td>$^{131}$I</td>
<td>8.0 d</td>
</tr>
<tr>
<td>$^{90}$Sr</td>
<td>51 d</td>
<td>$^{131m}$Te</td>
<td>78 h</td>
</tr>
<tr>
<td>$^{90}$Sr</td>
<td>29 a</td>
<td>$^{132}$I</td>
<td>2.3 h</td>
</tr>
<tr>
<td>$^{91}$Y</td>
<td>64 h</td>
<td>$^{133}$I</td>
<td>55 min</td>
</tr>
<tr>
<td>$^{91m}$Y</td>
<td>9.6 h</td>
<td>$^{133m}$Te</td>
<td>21 h</td>
</tr>
<tr>
<td>$^{92}$Sr</td>
<td>50 min</td>
<td>$^{134}$I</td>
<td>6.6 h</td>
</tr>
<tr>
<td>$^{92}$Y</td>
<td>2.7 h</td>
<td>$^{134}$Cs</td>
<td>30 a</td>
</tr>
<tr>
<td>$^{92}$Y</td>
<td>3.5 h</td>
<td>$^{135}$Ba</td>
<td>83 min</td>
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<tr>
<td>$^{93}$Y</td>
<td>10 h</td>
<td>$^{140}$Ba</td>
<td>1.3 d</td>
</tr>
<tr>
<td>$^{95}$Zr</td>
<td>64 d</td>
<td>$^{140}$La</td>
<td>1.7 d</td>
</tr>
<tr>
<td>$^{95}$Nb</td>
<td>35 d</td>
<td>$^{141}$La</td>
<td>3.9 h</td>
</tr>
<tr>
<td>$^{97}$Zr</td>
<td>17 h</td>
<td>$^{141}$Ce</td>
<td>33 d</td>
</tr>
<tr>
<td>$^{97m}$Nb</td>
<td>53 s</td>
<td>$^{142}$La</td>
<td>91 min</td>
</tr>
<tr>
<td>$^{99}$Mo</td>
<td>66 h</td>
<td>$^{142}$Ce</td>
<td>33 h</td>
</tr>
<tr>
<td>$^{99m}$Tc</td>
<td>6.0 h</td>
<td>$^{143}$Pr</td>
<td>14 d</td>
</tr>
<tr>
<td>$^{103}$Ru</td>
<td>39 d</td>
<td>$^{144}$Ce</td>
<td>280 d</td>
</tr>
<tr>
<td>$^{103m}$Rh</td>
<td>56 min</td>
<td>$^{144}$Pr</td>
<td>17 min</td>
</tr>
<tr>
<td>$^{105}$Ru</td>
<td>4.4 h</td>
<td>$^{147}$Nd</td>
<td>6.0 h</td>
</tr>
<tr>
<td>$^{105}$Ru</td>
<td>35 h</td>
<td>$^{147}$Nd</td>
<td>11 d</td>
</tr>
<tr>
<td>$^{106}$Ru</td>
<td>370 d</td>
<td>$^{149}$Pm</td>
<td>53 h</td>
</tr>
<tr>
<td>$^{106}$Pd</td>
<td>14 h</td>
<td>$^{149}$Nd</td>
<td>1.7 h</td>
</tr>
<tr>
<td>$^{112}$Ag</td>
<td>3.1 h</td>
<td>$^{151}$Pm</td>
<td>28 h</td>
</tr>
<tr>
<td>$^{113}$Cd</td>
<td>53 h</td>
<td>$^{153}$Sm</td>
<td>46 h</td>
</tr>
<tr>
<td>$^{113}$Cd</td>
<td>2.5 h</td>
<td>$^{237}$U$^a$</td>
<td>6.8 d</td>
</tr>
<tr>
<td>$^{117}$In</td>
<td>2.0 h</td>
<td>$^{238}$U$^b$</td>
<td>14 h</td>
</tr>
<tr>
<td>$^{121}$Sn</td>
<td>27 h</td>
<td>$^{240}$Np$^a$</td>
<td>7.2 min</td>
</tr>
<tr>
<td>$^{124}$Sb</td>
<td>2.8 a</td>
<td>$^{240m}$Np$^a$</td>
<td>2.4 d</td>
</tr>
<tr>
<td>$^{127}$Sn</td>
<td>2.1 h</td>
<td>$^{239-249}$Pu$^b$</td>
<td>24,000/6,600 a</td>
</tr>
</tbody>
</table>

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$^a$ Activation product.

$^b$ Fuel material. Only cumulative depositions and intakes over all tests were estimated.

Half-lives of radioactive Fe, Sb, Cs, and Pu are several years
Why does Fallout matter?

Radioactive decay can involve many steps before a stable species is formed.

Actinium series. The mass number of each element in the series is equal 4n+2. Where n is a positive integer.
Penetration abilities of different types of radiation

**Alpha Particles**
Stopped by a sheet of paper

**Beta Particles**
Stopped by a layer of clothing or less than an inch of a substance (e.g. plastic)

**Gamma Rays**
Stopped by inches to feet of concrete or less than an inch of lead

**Neutrons**
Stopped by a few feet of concrete
Impact on the environment

- Agricultural products
  - Interception
  - Yield
  - Translocation
  - Biological period
  - Fodder rates
  - Herds control

- Soils
  - Migration rate
  - Kind of soils
  - Soil/plant transfer

- Erosion
  - Slope
  - Rain
  - Land cover
  - Kind of soil

- Feeding
  - Food rates
  - Subsistence farming

- Deposition
  - Washout ratio
  - Kind of rains

- River banks
  - Slope
  - River bank vegetation
  - Type of soil

- Coastal areas
  - Dilution rates
  - Concentration factors
  - Biological yield

- River migration
  - Flow rate
  - Rate of MIE
  - Time period

Environmental Impact
Bioaccumulation: Coming full circle

Radiation & the environment: Assessing effects on plants and animals

An overview of a recent report issued by the United Nations Scientific Committee on the Effects of Atomic Radiation

MINI REVIEW
Consequences of nuclear accidents for biodiversity and ecosystem services
Henrik von Wehrden1,2, Joern Fischer2, Patric Brandt2, Viktoria Wagner3,4, Klaus Kummerer5, Tobias Kuemmerle6,7, Anne Nagel2, Oliver Olsson5, & Patrick Hostert6
Conservation Letts 2012. 1-9

Jun SASAKI,1 Kayoko HIRATANI,1 Itaru SATO,2 Hiroshi SATOH,3 Yoshitaka DEGUCHI,4 Hiroyuki CHIDA,5 Masahiro NATSUHORI,6 Takahisa MURATA,7 Kenji OCHIAI,1 Kumiko OTANI,8 Keiji OKADA9 and Nobuhiko ITO6
Unit for measuring radiation dose

- Amount of energy absorbed per unit weight of organ or tissue is absorbed dose and expressed a gray (Gy).
- 1 Gy = 1 joule radiation energy per kg organ/tissue
- 1 cGy = 1 rad

- Sievert (Sv) is absorbed dose x weighting factor of radiation (quality factor)
- 1 Sv = Dose (Gy) x rad weighting factor (WR)
Average annual dose to humans

Annual dose is 0.05 Sv (50 mSv)

- 10 Sv - Risk of death within days or weeks
- 1 Sv - Risk of cancer later in life (5 in 100)
- 100 mSv - Risk of cancer later in life (5 in 1000)
- 50 mSv – TLV annual dose for radiation workers in any one year
- 20 mSv – TLV annual average dose, averaged over five years
Biological effects of radiation

Time Scale (sec)

- $10^{-13}$
  - Modulation of Damage: Scavengers at Targets (DMSO, EtOH, etc.)
  - Events: Energy Absorption, Excitation, ionization

- $10^{-10}$
  - Radioprotectors (Thiols, Nitrooxides)
  - Secondary radicals (diffusible)

- $10^{-6}$
  - Chemical Repair (Thiols, Nitrooxides)
  - BIM radical, $O_2$, Modified Products

- $10^{-6}$ to $10^{-3}$
  - Enzymatic Repair
  - DNA breaks, Proliferation/degeneration

- Seconds to Years
  - Mutation/carcinogenesis, Cell death
Possible outcomes of radiation damage

- Radiation
- Diverse outcomes:
  - Normal cells produced
  - NO PROBLEM
  - NO PROBLEM
  - Damaged cell dies
  - Cells may completely repair themselves
  - Aneuploidy
  - Chromosome aberrations
  - Mutations
  - Micronuclei
Acute Radiation Syndrome – what is it?

- Radiation dose dependent injuries to cells, tissues, and organs
- Spectrum of injuries and symptoms – multi-organ dysfunction/failure
Tissue sensitivity to radiation

- Lymphocytes
- Granulocytes, Erythrocytes
- Epithelial cells
- Endothelial cells
- Connective tissue
- Bone cells
- Nerve
- Brain
- Muscle

- Bergonie and Tribondeau, 1906
Scientific areas

- CNS
- Kidney
- Lung
- Cardiovascular
- Cutaneous
- Hematopoietic (H)
- Gastrointestinal (GI)

Decoration of internal radionuclide contamination

MCMs for acute (ARS) and delayed syndromes

Biodosimetry

Combined injuries
What does RNCP do?

• MCMs to treat or mitigate radiation injury 24 hours post-exposure
• Drugs to remove radioactive materials from the body
• Biodosimetry tools and biomarker identification to determine levels of radiation exposure
NIAID-RNCP: Program Elements

Universities
CMCRC, Pilot Projects
Contacts/Presentations
Candidate Efficacy Screen
Optimization/Development

Inter/Intra-agency Collaborations
HHS/BARDA
DoD/AFRRI
NCI
NCATS BrIDGs
NIA
NIDDK

FDA Regulatory
In-house guidance

Company Collaborations
SBIR program
Contacts/Presentations
Candidate Efficacy Screen
Optimization/Development

Grants
Immune Reconstitution
GI, Lung, Combined Injury MCMs
Oral Deporation Agents
Predictive Biodosimetry

International Collaborations
Global Health Security Initiative (GHSI)
REMPAN/WHO
International Symposia
Institut de Radioprotection et de Sûreté Nucléaire (IRSN)

Contracts
Product Development Support & Animal Model Development
Oral Forms of DTPA
Radiation Effects Research Foundation (RERF)
GI, Lung and Platelet MCMs
NIAID Radiation and Nuclear Countermeasures Program

Biodosimetry Architecture

Immediate triage

Medical management

Risk assessment

Dose estimation
TBI vs PBI
Specific tissue Damage

POC devices
Hematology
OSL/EPR
qPCR
Biomarkers

Predictive Biodosimetry

>2 Gy

<2 Gy

Contamination

Decorporation agents

Cytogenetics
Micronucleus Assay

Predictive Biodosimetry
Novel biodosimetry approaches

**Novel Biodosimetry Approaches**

**Telomere shortening**

**Senescence Chips**

**Prediction of Neutropenia**

**Microfluidic technology using Aptamers**

**Radiation dose using urine metabolomics**

**Figure 1.** Senescence-chip for radiation biodosimetry as well as medical countermeasure.

**From Pannikul et al. Metabolites 2019**
Identify and develop radiation countermeasures for radiation subsyndrome of heme-ARS

Polypharmacy approach for heme-ARS

Survival Distribution Function

- Control (D5W)
- Pegfilgrastim (300mcg/kg, d1 & d8)

Survival curves for different groups:
- CA
- D
- GM
- IL-11
- G + GM
- G + IL-11
- G + S
- G + S
- G + GM + IL-11

Survival rates over days:
- Vehicle
- PLX 200h & 5d
- PLX 48h & 5d
- PLX 72h & 5d
Identify and develop radiation countermeasures for radiation subsyndromes of Lung, Kidney, Skin.
NHP survivor cohort (Natural history)

- Cohort initiated in 2005
- Wake Forest only provider
- Animals “adopted” from USG-funded studies
- >140 irradiated NHPs
- >30 unirradiated control NHPs
- Sample/data sharing
- Unanticipated late effects
  - Diabetes
  - Immune blind spots
  - Multiple comorbidities
Oral decoration products

- **3,4,3-LI(1,2-HOPO)**
  - LBNL (grant, PDSS Contract)
  - For U and transuranics

- **Zn-DTPA Tablets**
  - SRI International
  - For transuranics

- **C2E2**
  - Capture Pharmaceutics (via UK, UNC)
  - For transuranics
Nuclear fallout modeling (IAA with NCI)

Cumulative Cs-137 deposition (Bq/m²) from NTS

Cumulative Cs-137 deposition (Bq/m²) from Global fallout
Long term monitoring, dose reconstruction, and Retrospective Biodosimetry

Chromosome Translocations, Inversions, and Telomere Length for Retrospective Biodosimetry on Exposed US Atomic Veterans

(accepted for publication – Radiation Research)
Miles J. McKenna¹,², Erin Robinson³, Lynn Taylor³, Christopher Tompkins³, Michael N. Cornforth³,⁴, Steven L. Simon⁵ and Susan M. Bailey¹,²,³

Estimation of Radiation Doses to U.S. Military Test Participants from Nuclear Testing: A Comparison of Historical Film-Badge Measurements, Dose Reconstruction, and Retrospective Biodosimetry

[Journal (Radiation Research) review completed]
Steven L. Simon¹, Susan M. Bailey³, Harold L. Beck⁶, John D. Boice⁴, André Bouville¹, Aaron B. Brill⁵, Michael N. Cornforth⁶, Peter D. Inskip⁵, Miles J. McKenna², Michael T. Mumma², Silvia I. Salazar⁷, Abigail Ukwuani¹

In this issue, companion articles by: Simon et al., “Estimation of Radiation Doses to U.S. Military Test Participants from Nuclear Testing: A Comparison of Historical Film-Badge Measurements, Dose Reconstruction, and Retrospective Biodosimetry.”
McKenna et al., “Chromosome Translocations, Inversions and Telomere Length for Retrospective Biodosimetry on Exposed U.S. Atomic Veterans.”
RNCP advances

- Product licensures
  - Neupogen®
  - Neulasta®
- IND/IDE approvals
  - 2 MCMs
  - 3 oral decoporation
  - 4 biodosimetry
- 15 pre-IND/pIND sponsor meetings with FDA
- Interactions with 275+ companies
- 29 products transitioned to BARDA
Radiation and emergency response

- The CDC Public Response Source at 1-888-246-2675
- Conference of Radiation Control Program Directors (CRCPD) at www.crcpd.org or 502-227-4543

**Acute Radiation Syndrome** (continued from previous page) Reviewed and updated May 20, 2005 Page 2 of 2

- U.S. Environmental Protection Agency (EPA) at www.epa.gov/radiation/rert
- Nuclear Regulatory Commission (NRC) at www.nrc.gov or 301-415-8200
- Federal Emergency Management Agency (FEMA) at www.fema.gov or 202-646-4600
- Radiation Emergency Assistance Center/Training Site (REAC/TS) at www.orau.gov/reacts or 865-576-3131
- U.S. National Response Team (NRT) at www.nrt.org
- U.S. Department of Energy (DOE) at www.energy.gov or 1-800-dial-DOE
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