Emergency Biodosimetry

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Website for research program:
www.usuhs.edu/afrri/research/biodos.htm
Website for biodosimetry tools:
www.usuhs.edu/afrri/outreach/biodostools.htm
### Financial Interest, Other Relationship Disclosures, and Disclaimer

<table>
<thead>
<tr>
<th>Commercial Manufacturer</th>
<th>Financial Interest</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioRad, Careside, etc.</td>
<td>None</td>
<td>Equipment evaluation</td>
</tr>
<tr>
<td>Various companies developing 1&lt;sup&gt;st&lt;/sup&gt; responder software applications</td>
<td>None</td>
<td>Interactions with Technical Support Working Group developers</td>
</tr>
<tr>
<td>Meso Scale Diagnostics</td>
<td>None</td>
<td>Co-Investigator on BARDA contract to develop radiation responsive biomarker device for radiation dose assessment</td>
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</table>

The opinions, conclusions, and recommendations expressed or implied do not necessarily reflect the views of the Department of Defense or any other department or agency of the federal government.
Taskings

• What are the current recommended applications of biodosimetry in a nuclear power plant accident for workers, accident responders, and general public that are suspected of exposure to radiation?

• Describe the concept of operations for biodosimetry.

• What are the current limitations and gaps in biodosimetry?
Guidance and Doctrine – I
Multiple Parameter Biodosimetry
Guidance and Doctrine – II
Multiple Parameter Biodosimetry
Nuclear Reactor Accidents

Biodosimetry for potential radiation overexposures involving:

- Nuclear Power Plant Workers
- Accident Responders
- Local Population

Biodosimetry – General Guidance

• Perform measurements, if appropriate, to determine radionuclide contamination and record physical dosimetry measurements, if available
• Observe and record prodromal signs (erythema) and symptoms
• Obtain CBC with white blood cell differential immediately, then every 6 hours for 2-3 days, and then twice a day for 4 days
• Sampling blood for the chromosome-aberration cytogenetic bioassay using the “gold standard” dicentric assay (or other suitable cytogenetic chromosome aberration assay)
• Bioassay sampling from various sources (i.e., urine, fecal, blood, nasal, oral, etc.), if appropriate, to determine radionuclide contamination
• Biosampling blood for measurement of clinical blood chemistries, proteomic, and gene-expression radiation-responsive biomarkers
• Biosampling nail clippings for measurement of free radicals by electron paramagnetic resonance (EPR)
• Consider other opportunistic dosimetry approaches as available

# Acute-phase Patient Assessment Methods

<table>
<thead>
<tr>
<th>Assessment Method</th>
<th>Parameters for considering assessment method for use in early (&lt;5 d) triage screening</th>
<th>Applicable for scoring ARS severity</th>
<th>Dose (Gy) or ARS response category level to select for priority cytogenetic triage analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Recording of Location History</td>
<td>Time for analysis</td>
<td></td>
<td>Triage dose, Gy</td>
</tr>
<tr>
<td>Direct Observation of Clinical Signs and Symptoms</td>
<td>Estimate cost per sample, US Dollars</td>
<td></td>
<td>Response category levels</td>
</tr>
<tr>
<td>Personal Monitoring (Direct, non invasive)</td>
<td>&lt; 2 min</td>
<td></td>
<td>3-7</td>
</tr>
<tr>
<td>- in vivo EPR</td>
<td>&lt; 5 min</td>
<td></td>
<td>3-7</td>
</tr>
<tr>
<td>- portable hand held meters (triage/screening)</td>
<td>&lt; 2 min</td>
<td></td>
<td>3-7</td>
</tr>
<tr>
<td>- portal monitors (triage/screening)</td>
<td>&lt; 2 min</td>
<td></td>
<td>3-7</td>
</tr>
<tr>
<td>- whole-body counting</td>
<td>&gt; 25 min</td>
<td></td>
<td>3-7</td>
</tr>
<tr>
<td>Personal Monitoring (Indirect, invasive)</td>
<td>&lt; 3 min</td>
<td>$2</td>
<td>3-7</td>
</tr>
<tr>
<td>- blood chemistry (i.e., CRP, amylase activity)</td>
<td>&lt; 2 min</td>
<td>$1</td>
<td>3-7</td>
</tr>
<tr>
<td>- CBC and differential/lymphocyte count</td>
<td>&lt; 15 min</td>
<td>Unknown</td>
<td>3-7</td>
</tr>
<tr>
<td>- nasal swab</td>
<td>&gt; 1 d</td>
<td>50 pCi/swab</td>
<td>3-7</td>
</tr>
<tr>
<td>- stool sample</td>
<td>&gt; 1 d</td>
<td>5 pCi/g</td>
<td>3-7</td>
</tr>
<tr>
<td>- urine sample (spot; 24-hr)</td>
<td>&lt; 1 d; &gt; 1 d</td>
<td>30 pCi/vial</td>
<td>3-7</td>
</tr>
<tr>
<td>- cytogenetics (i.e., 20-50 metaphase triage; 1000 metaphase analysis)</td>
<td>&gt;3 days</td>
<td>1 Gy; 0.2 Gy</td>
<td>3-7</td>
</tr>
<tr>
<td>Area Monitoring</td>
<td>Unknown</td>
<td></td>
<td>3-7</td>
</tr>
<tr>
<td>- dosimetry results (e.g. TLDs, aerial measurements) combined with personal location information</td>
<td>Unknown</td>
<td></td>
<td>3-7</td>
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</tbody>
</table>
Medical Recording Worksheets and Software Tools

AFRRI website: www.usuhs.edu afrri/

REMM website: www.remm.nlm.gov/index.html
**Biodosimetry Concept of Operations**

Radiation Patient Assessment Algorithm – Medical Recording

Access and Stabilize Life Threatening Problems

Yes

Externally Contaminated?

No

**Medical Recording:**
- Radiation Survey
- Radiobioassay Sampling

**Initial Decontamination, Access and Treat Life-Threatening Medical Problems, and Stabilize Patient**

Follow-up Radiation Exposure Assessment

**Prioritize Decontamination and Decontaminate**

**Initial Radiation Exposure Assessment**

**Medical Recording:**
- Clinical Signs & Symptoms
- Haematology
- Blood Chemistries
- Radiobioassay Sampling
- Alternate Radiation Screening Assessment Assays

Medical Recording:
- Radiation Survey
- Radiobioassay Sampling

Emergency Medical Response Organization Radiological Assessment

- On-scene controller
- First responder
- Medical response initiator
- Emergency medical responder
- Emergency medical manager
- Ambulance transport team
- Hospital emergency department response team
- Medical specialist of appropriate service
- Referral hospital
- Public health advisor
- **Radiological assessor**
- **Health/medical physicist**
- **Decontamination team**
- Public health advisor
- Medical support team
- **Biodosimetry team**

Survey meters

Personnel dosimeters
AFRRI
WinFRAT
First-responders Radiological Assessment Triage

Data Entry and Report
- Enter Signs and Symptoms
- Enter Lymphocyte Counts
- Enter Desimetry and/or Contamination

Display Multiparameter Triage Dose Assesment

Signs and Symptoms
- Vomiting
- Diarrhea
- Convulsion
- Tachypnea
- Headache
- Impaired Consciousness
- Elevated Body Temperature

Dosimetry Information
- Yes
- No
- Unknown

Triage Dose Assessment
- Category
- Estimated dose (cSv)
- Pooling

Vomiting
- Time of onset after exposure:
  - Within 30 minutes
  - 30-40 minutes
  - 41-60 minutes
  - 1-1.5 hours
  - 1.5-2.5 hours

Diarrhea
- Time of onset after exposure:
  - Less than 1 hour
  - 1-2 hours

Triage Dose Assessment - 1
- Radiation OVEREXPOSURE - potentially SEVERE medical effect.

Triage Dose Assessment - 2
- POOR to MODERATE reliability
HemoCue® WBC Systems

www.hemocue.com/us/Products/White_Blood_Cell_count-220.html
Biodosimetry Based on Hematology

Lymphocyte Counts

Neutrophil to Lymphocyte Ratio

![Graph showing lymphocyte counts and neutrophil to lymphocyte ratio over time and dose. The x-axis represents time after exposure in days, the y-axis represents lymphocyte count in $10^9$ L$^{-1}$, and the z-axis represents ratio. Doses range from 2 Gy to 8 Gy.]
Radiological Triage Concept Using CRP
(Ossetrova and Blakely)

Rapid FDA Approved Devices

Orion CRP Quick Kit

Stanbio Laboratory CRP test kit

Low human baseline levels

![Graph showing C-reactive Protein (NHANES III)](http://www.mylaboratoryquality.com)
Radiological Triage Concept Using CRP (Ossetrova and Blakely)

**High signal to noise**

![Graph showing CRP content over time after irradiation for males and females.]

**ARS Bioindicator**

Prognosis for ARS based on CRP level in serum of blood of people damaged at Chernobyl NPP accident during primary reaction (3-9 days after irradiation).

<table>
<thead>
<tr>
<th>Degree of ARS</th>
<th>CRP level ≥ 1 mm</th>
<th>CRP level: 0.5 mm</th>
<th>CRP level 0 mm</th>
<th>Total (row)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4</td>
<td>26</td>
<td>9</td>
<td>17</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>7</td>
<td>19</td>
<td>32</td>
</tr>
<tr>
<td>0-1</td>
<td>3</td>
<td>18</td>
<td>23</td>
<td>44</td>
</tr>
<tr>
<td><strong>Total (column)</strong></td>
<td><strong>35</strong></td>
<td><strong>34</strong></td>
<td><strong>59</strong></td>
<td><strong>128</strong></td>
</tr>
</tbody>
</table>

Blakely *et al.*, Health Physics, FEB 2010

Radiation Protein Biomarker Concept
Dose Response

Acute Injury Biomarkers

ARS Organ Injury Biomarkers


METREPOL PLUS
(Sequential Diagnostic)

**Biomarkers (organ specific)**
- **Neurovascular System:** Oxysterol 24S-hydrocholesterol
- **Haematopoietic System:** Fit-3 ligand, TPO, EPO, IL-6, G-CSF
- **Cutaneous System:** IL-1, IL-6, Tumor necrosis factor, GM-CSF, TGF-β, Intracellular adhesion molecule, MMP
- **Gastrointestinal System:** Serum or urinary amylase activity, Citrulline, Neurotension, Gastrin hormones, CRP, SAA, Oxysterol 71-hydroxycholesterol

**Clinical Symptoms**
- Nausea, Vomiting, Anorexia, Fatigue syndrome, Fever, Headache, Hypotension, Neurological deficits, Cognitive deficits, Lymphocytes changes, Granulocyte changes, Thrombocyte changes, Blood loss, Infection, Erythema, Sensation / itching, Swelling and Oedema, Blistering, Desquamation, Ulcer / Necrosis, Hair loss, Onycholysis, Diarrhoea, Abdominal Cramps / Pain

**Grading code (organ specific)**

<table>
<thead>
<tr>
<th>N</th>
<th>H</th>
<th>C</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2</td>
<td>H3</td>
<td>C1</td>
<td>G2</td>
</tr>
</tbody>
</table>

**Response Category**

RC = ?_{xd}

**Example:**

RC = 3_{2d}

**N2**

Capital letter for the organ system, e.g. neurovascular system

**N2 H3 C1 G2**

An RC equal to 3 was determined on the second day after exposure

**Degree of severity to describe the extent of damage**

N = Neurovascular System
H = Haematopoietic System
C = Cutaneous System
G = Gastrointestinal System
i = Degree of severity 1-4
xd = Time point (x) at which RC was established; measured in days (d) after begin of exposure.

Multiple Parameter Radiation Biodosimetry

EPR Dosimetry
- In vivo
- Ex vivo

Bioassays to determine radionuclide contamination
- Urine
- Fecal
- Blood
- Nasal
- Oral

Cytogenetic Assays
- Dicentric chromosome aberrations
- Premature chromosome condensation
- Micronuclei
- Foci of radiation-induced proteins

Plucked hairs
Cheek cells
Skin
Blood


Strategies to Enhance Rapid Throughput for Cytogenetic Biodosimetry

- National expert cytogenetic biodosimetry laboratories
  - REAC/TS; AFRRI (USA)
- Triage and/or dicentric chromosome aberration (DCA) QuickScan scoring
  - Lloyd (UK); Wilkins (Canada)
- Use of commercial off-the-shelf automation devices (metaphase harvesters, metaphase spreaders, metaphase finders) and automated scoring
  - Prasanna, Ramakumar, and colleagues (AFRRI)
  - Romm and colleagues (Germany)
- An internet-based strategy to score digitized electronic images
  - Livingston and colleagues (REAC/TS)
- Development of a network of reference and supplementary national and international cytogenetic biodosimetry laboratories
  - UK/France/Germany; Japan; Canada; USA; Latin America; South Korea
Lymphocyte - Dicentric Assay

Effect of Age and Low-Radiation Doses

Dose Response Calibration Curve

Lymphocyte - Dicentric Assay

Early Dicentric Yields: Grade of ARS Severity (Chernobyl)

Cytogenetic Doses for Fukushima Daiichi Nuclear Power Stations Restoration Workers <0.3 Gy


At present there is no FDA approved biodosimetry device.

We need the capabilities to assess exposure, dose level, and the extent of potential radiation injury for: a) operational, b), early-phase medical treatment, and c) late-effects monitoring decisions.

We use physical dosimeters, if available, to “assess” exposure and dose; FDA does not require that these devices be regulated for this purpose.

Our concept of operations involves use of a FDA approved biodosimetry device to guide early treatment decisions.

Risk of radiation-induced lethality is significantly influenced by partial-body exposures, dose rate, and radiation quality, which limits “dose” alone as a guide for medical intervention for life-savings measures (i.e., G-CSF treatment).

Use of a multi-parameter based diagnostic approach including the use of biological indicators of radiation injury severity is recommended for biodosimetry device used for early-phase medical treatment decisions.
Additional Gaps and Limitations in Biodosimetry Capability

- Rapid assays to assess partial-body exposures
- Operational biodosimetry personnel and resources:
  - Enhanced assess to deployable radiological teams with capabilities to perform on-site haematology, assessment of clinical signs and symptoms, and sampling for radiobioassays
  - Protocols, personnel, and resources for exposure assessment of potentially exposed populations for health risk study*
  - Funding to establish and sustain functional national and global networks of expert reference laboratories performing dose assessment

*See Bouville et al. Environ Health Perspectives 122(1):1-5, 2014
“If you fail to plan, you are planning to fail!”

Benjamin Franklin