IRPA 12
BUENOS AIRES - ARGENTINA - 19 / 24 OCTOBER 2008
12TH INTERNATIONAL CONGRESS OF THE INTERNATIONAL RADIATION PROTECTION ASSOCIATION
REFRESHER COURSE (RC-12): 8:00 to 9:00 AM, Thursday 23 Oct 2008

Biological Dosimetry.
Early Biodosimetry Response:
Recommendations for Mass-Casualty Radiation Incidents and Terrorism

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of the Health Sciences
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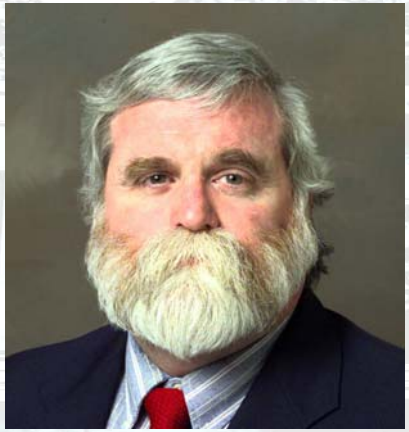
Speaker Biosketch
William F. Blakely, Ph.D

- **Radiobiologist**
- **Biological Dosimetry Research Group, Advisor**
  - **-Armed Forces Radiobiology Research Institute (AFRRI), Uniformed Services University of the Health Sciences (USUHS)**
- **Course Director, Radiation Biology (PMO-582), USUHS**
- **USA representative**
  - **-ISO TC85/SC2 (Radiation Protection) Working Group 18 (performance criteria for service laboratories performing biological dosimetry by cytogenetics)**
- **Project Manager**
  - **-Radiation Casualty Management software application (Biodosimetry Assessment Tool)**
- **Community of Science expertise profile**
  - **- http://myprofile.cos.com/wfblakely**



Financial Interest or Other Relationships Disclosure

Commercial Manufacturer	Financial Interest	Other Relationship
BioRad, Careside	None	Equipment evaluation
Various companies developing 1st responder software applications	None	Interactions with Technical Support Working Group developers

Patent Title	Status
Biomarker Panels For Assessing Radiation Injury And Exposure	International PCT application filed 6-12-07; WH 2001797.121 PCT/US2007/013752, Institution-owned, United States of America.
A simple and rapid method to induce premature chromosome condensation in human resting peripheral blood lymphocytes, to study structural and numerical chromosomal aberrations involving specific chromosomes	Provisional patent, 2001, International PCT application filed. Institution-owned, United States of America.
Mouse genomic DNA hybridization probe an immunoenzymatic color pigment detection of mouse bone marrow micronucleus for regulatory required genetic toxicity assay (mouse bone marrow micronucleus assay)	Provisional patent filed, 2000, Institution-owned, United States of America.

AFRRI supported this research under work unit BD-2 and -10.

Coworkers and Collaborators

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Refresher Course Objectives

- **Address biodosimetry approach to prepare and respond to a mass-casualty radiological event**
- **Give an overview of the generic multiparameter and early-response approach for radiation biodosimetry**
- **Review fundamental components for early-response multi-parameter biodosimetry with examples using medical recording tools and briefly address provisional and emerging radiation injury and dose assessment triage assays**
- **Provide recommendations for biodosimetry enhancements for mass-casualties radiological incidents**

Abstract

BiodosEPR-2006 Meeting: Acute Dosimetry Consensus Committee Recommendations on Biodosimetry Applications in Events Involving Uses of Radiation by Terrorists and Radiation Accidents

By George A. Alexander, Harold M. Swartz, Sally A. Amundson, William F. Blakely, Brooke Buddemeier, Bernard Gallez, Nicholas Dainiak, Ronald E. Goans, Robert B. Hayes, Patrick C. Lowry, Michael A. Noska, Paul Okunieff, Andrew L. Salner, David A. Schauer, Francois Trompier, Kenneth W. Turteltaub, Phillipe Voisin, Albert L. Wiley, Jr., Ruth Wilkins

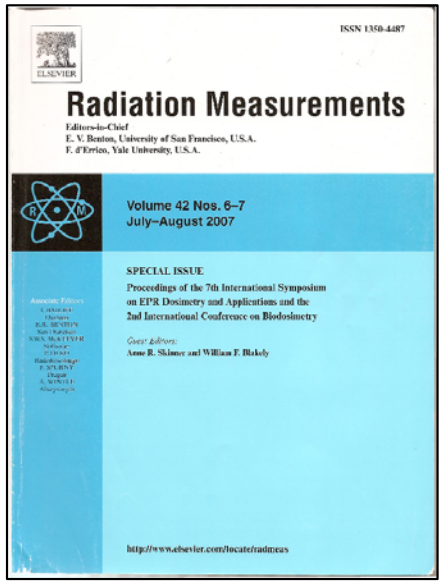
1. **Introduction and requirements for acute dosimetry**
2. **Current status of biodosimetry methods for radiation incidents and accidents**

2.1 Cytogenetics

2.2 Electron paramagnetic resonance

2.3 Other approaches and technologies

3. **Recommendations and summary**



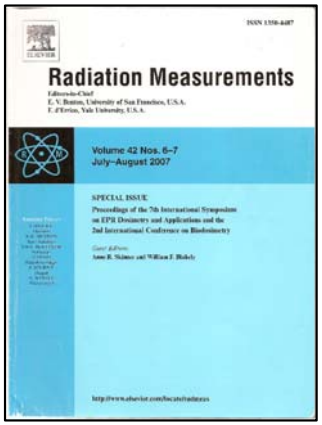
Vol. 42(6-7): 972-996, 2007

1. Introduction

BiodosEPR-2006 Meeting: Acute Dosimetry Consensus Committee Recommendations on Biodosimetry Applications in Events Involving Uses of Radiation by Terrorists and Radiation Accidents

Appendices

A. Review of Medical Devices for Dose Assessment by the US Food and Drug Administration
B. Current Practice of Cytogenetic Biodosimetry for Radiation Incidents and Accidents
C. Current Status of Deployable Mitigating Agents
D. Bioassay Sampling for Radioactivity
E. Provisional EPR Biodosimetry Protocols for Use in Radiation Incidents and Accidents
F. Procedures for Collecting Blood for Hematology, Chromosomal, and Blood Chemistry Analyses.
G. Radiological Exposure Scenarios
H. Acute Radiation Syndromes
I. Dose Estimation Based on Location History
J. Summary of Prior Uses of Biodosimetry



Vol. 42(6-7): 972-996, 2007

1. Introduction

Acute-phase Cytogenetic Biodosimetry in Radiation Accidents

Accident location	Year of accident	Number of people exposed	Dicentrics	PCC	References
Cuidad Juarez, Mexico	1984	~ 7	7?	N/A	Littlefield et al. (1989)
Chernobyl, Russia	1986	116,000	158	N/A	Sevan'kaev (2000)
Goiânia, Brazil	1987	250	129	N/A	Ramalho and Nascimento (1991)
Lilo, Georgia	1986–1987	Multiple	4	N/A	Roy et al. (2006)
Kiisa, Estonia	1994	4	4	N/A	Lindholm et al. (2002)
Istanbul, Turkey (multiple cases)	1995	21	21	18?	Koksal et al. (1995)
Tokaimura, Japan	1999	3	1	3	Kanda et al. (2002)
					Hayata et al. (2001), and
					Sasaki et al. (2001)
		Unknown	43		
Meet Halfa, Egypt	2000	7	5	N/A	El-Naggar et al. (2002)
Bangkok, Thailand	2000	~ 28	28	28	Jinaratana (2002)
Gent, Belgium	2005	1	1	1	Thierens et al. (2005)
Referral Laboratory—incident summary	2003–2005	23	18	Uncertain	Lloyd et al. (2006)
Referral Laboratory—incident summary	1968–2003	996	996	Uncertain	Lloyd et al. (2006)
Cytogenetic reference standards	2002				Voisin et al. (2002)

[a]Table expanded from earlier work by Prasanna and colleagues (Prassanna et al., 2004).

Alexander et al., Radiation Measurements 42: 972-996, 2007.

1. Introduction

Acute-phase Dose Assessment by EPR in Radiation Accidents

Place of accident	Date	Type of accident	Materials
USA	1991	Accelerator; various radiation accidents	EPR (bone; digits), Schauer et al. (1993, 1994, 1996), and Romanyukha et al. (2005)
San Salvador	1991	Co-60 irradiator	EPR (bone; femur), Desrosiers (1991)
Tammiku, Estonia	1994	RED	TL (quartz pots), EPR (sugar samples), Hutt et al. (1996)
Georgia	2001	RED	Clairand et al. (2006)
Review of general and combined acute-phase accident dosimetry	2005	Overview of acute-phase dosimetry	Swartz et al. (2005), Blakely et al. (2002a,b, 2005), Trompier et al. (2006), and Kleinerman et al. (2006)

Alexander et al., Radiation Measurements 42: 972-996, 2007.

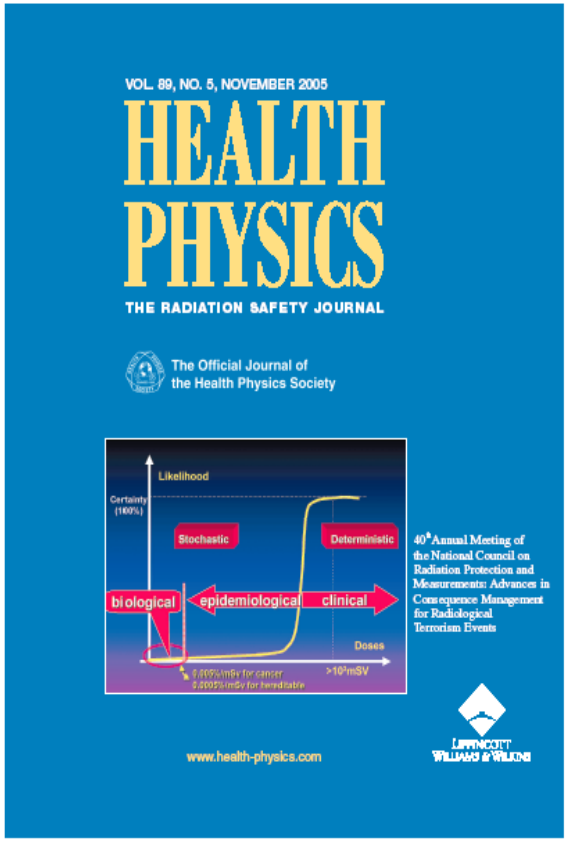
1. Introduction

Fortieth Annual Meeting April 14-15, 2004

Advances in Consequence Management for Radiological Terrorism Events

Major Topics/Sessions

- Radiological Terrorism – Introduction and Preparedness
- Medical Management of Radiological Terrorism Events
- Research Advances in Biodosimetry, Radiation Prophylactic, and Therapeutic Strategies
- Consequence Management Strategies



1. Introduction

Health Phys. 89(5): 415-600, Nov 2005

Radiological Threat

Table 2. Seizures of radioactive material.

Date	Location	Material
14 November 2002	Tanzania	Uranium
20 September 2002	Ukraine	Strontium-90 (1 source)
10 June 2002	Russia	Uranium (2 kg)
30 May 2002	Lithuania	Cesium-137 (1 kg)
15 May 2002	Bulgaria	Plutonium-239
1 May 2002	Belarus	Cesium-137 (6 sources)
7 April 2002	Chechnya	Cesium-137 (10 sources)
5 April 2002	Uganda	Cobalt-60 (1 source)
25 March 2002	Tajikistan	Uranium (639 g)
25 March 2002	Afghanistan	Cobalt-60

"Because of recent terrorist activities and intelligence information, there is strong sentiment that it is not a question of if, but when, a radiological or nuclear terrorist attack will occur."

- W.C. Conklin, Federal Emergency Management Agency

- P.L. Liotta, U.S. Navy, Armed Forces Medical Intelligence Agency

Health Physics 89(5): 415-470, 2005

Early Biodosimetry Response: Recommendations for Mass-Casualty Radiation Incidents and Terrorism

2. Biodosimetry preplanning

- Radiation exposure assessment methods
- Radiation/radiological response teams and networks

3. Biodosimetry – concept of operations

- Stockpiling of reagents and equipment
- Selection of appropriate triage, clinical, and definitive assays
- Establishment and exercise of specialize response teams

4. Early-response multiple parameter biodosimetry

- Medical recording for radiation incidents
- Triage biodosimetry

Direct Recording of Location History
Direct Observation of Clinical Signs and Symptoms
Personal Monitoring (Direct, non invasive)
- *in vivo* EPR
- portable hand held meters (triage/screening)
- portal monitors (triage/screening)
- whole-body counting
Personal Monitoring (Indirect, invasive)
- blood chemistry (*i.e.*, amylase activity)
- CBC and differential/lymphocyte count
- *in vitro* EPR (i.e., nails)
- nasal swab
- stool sample
- urine sample (spot; 24-hr)
- cytogenetics (i.e., 20-50 metaphase triage; 1000 metaphase analysis)
Area Monitoring
- dosimetry results (e.g. TLDs, aerial measurements) combined with personal location information

Acute-phase patient assessment methods

- Assay parameters to consider for triage screening
- Assays useful for scoring ARS severity levels
- Assay dose and ARS response severity levels that permit prioritization for cytogenetic chromosome aberration triage analysis

Alexander et al., Radiation Measurements 42: 972-996, 2007.

2. Biodosimetry preplanning

Table I. Acute-phase patient assessment methods.*

Assessment Method	Parameters for considering assessment method for use in early (<5 d) triage screening			Applicable for scoring ARS severity	Dose (Gy) or ARS response category level to select for priority cytogenetic triage analysis	
	Time for analysis	Estimate cost per sample, US Dollars			Triage dose, Gy	Response category levels
Direct Recording of Location History	< 2 min	-			3-7	
Direct Observation of Clinical Signs and Symptoms	< 5 min	-		Yes	3-7	1-4
Personal Monitoring (Direct, non invasive)						
- *in vivo* EPR	Unknown	Unknown			3-7	
- portable hand held meters (triage/screening)	< 5 min	-			-	
- portal monitors (triage/screening)	< 2 min	-			-	
- whole-body counting	> 25 min	-			-	
Personal Monitoring (Indirect, invasive)		**Detection limit,#**	**Estimate cost per sample, US Dollars#**			
- blood chemistry (*i.e.*, amylase activity)	< 3 min		<$2		3-7	
- CBC and differential/lymphocyte count	< 2 min		<$1	Yes	3-7	1-4
- *in vitro* EPR (i.e., nails)	<15 min		Unknown		3-7	
- nasal swab	> 1 d	50 pCi/swab	$70		-	
- stool sample	> 1 d	5 pCi/g	$80		-	
- urine sample (spot; 24-hr)	< 1 d; > 1 d	30 pCi/vial	$90		-	
- cytogenetics (i.e., 20-50 metaphase triage; 1000 metaphase analysis)	>3 days	1 Gy; 0.2 Gy	Unknown; $500-3,000		-	
Area Monitoring						
- dosimetry results (*e.g.* TLDs, aerial measurements) combined with personal location information	Unknown	-			3-7	

*The Table was modified a version reported by Alexander and colleagues [2].

Note that the personal and area monitoring methods are listed in alphabetical order and, therefore, their location in the table does not infer priority or preference.

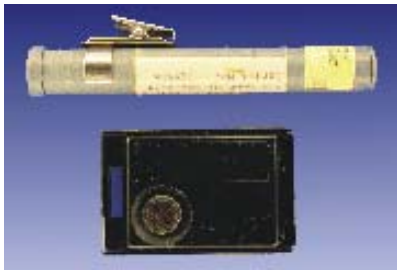
Radiobioassay detection limits and costs are based on ^{137}Cs isotope and 1 min gamma-ray spectrometry analysis with high priority count (costs 3-times routine) with no automatic sample changers used. Detection limits for cytogenetic analysis are presented in acute photon equivalent dose in units of Gy.

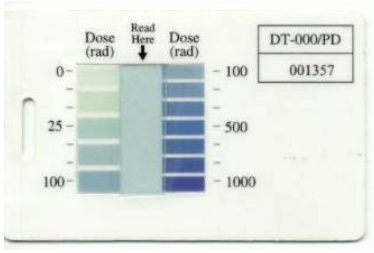
2. Biodosimetry preplanning

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





(LOCCSID)

Personnel dosimeters

2. Biodosimetry preplanning

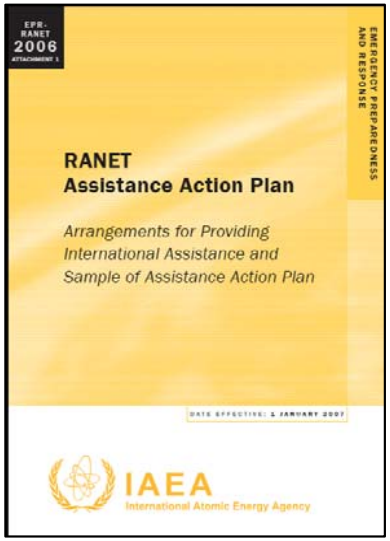
Table II. Selected List of Radiological Response Teams	
Initial Assessment	Nuclear, Chemical, and Biological
Radiation Source Search	Medical Recording and Registry
Radiation Survey and Bioassay Sampling	Haematology and Cytogenetic Biodosimetry Sampling

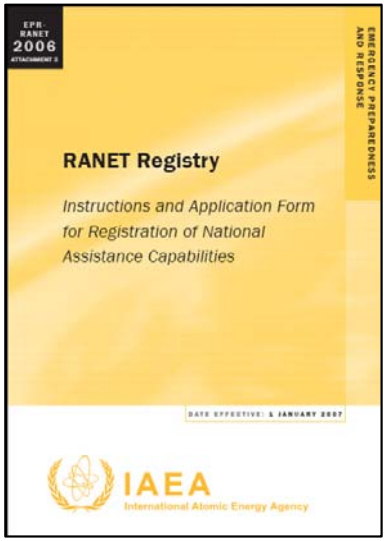
2. Biodosimetry preplanning

IAEA's National Assistance Capabilities

Aerial survey	Public health protection
Radiation monitoring	Biodosimetry
Environmental measurements	Internal dose assessment
Source search/recovery	Bioassay
Assessment and advice	Histopathology
Medical support	Dose reconstruction

Includes Cytogenetic Biodosimetry Capability





2. Biodosimetry preplanning

Strategies to Enhance Rapid Throughput for Cytogenetic Biodosimetry

- **Establishment of one or more national expert cytogenetic biodosimetry laboratories**

  - REAC/TS (USA)

- **Use of commercial off-the-shelf automation devices (metaphase harvesters, metaphase spreaders, metaphase finders)**

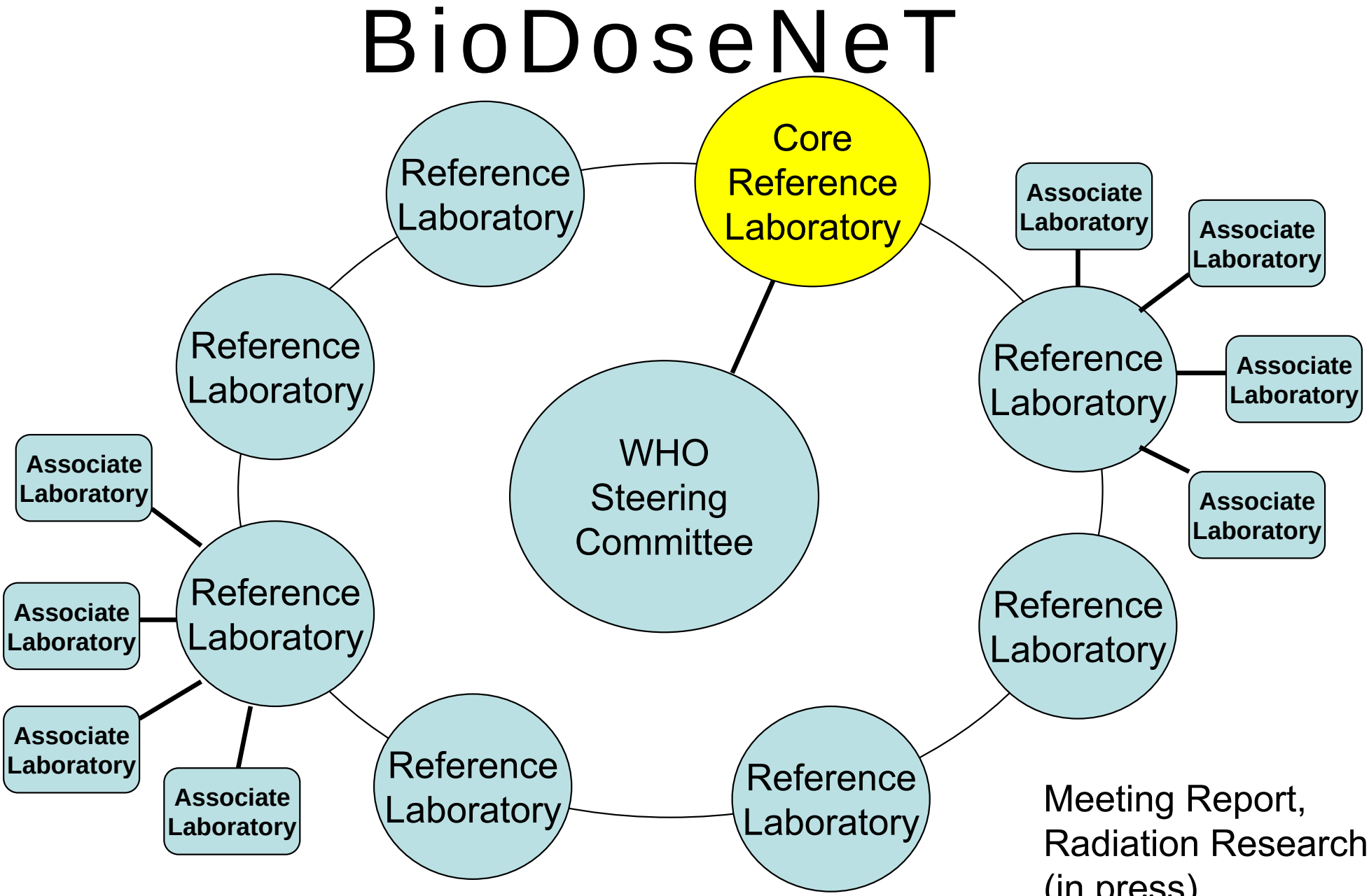
  - Prasanna and colleagues (AFRRI)

- **Development of a network of reference and supplementary national and international cytogenetic biodosimetry laboratories**

  - UK/France/Germany; Japan; Canada; USA; Latin America; South Korea

2. Biodosimetry preplanning

World Health Organization

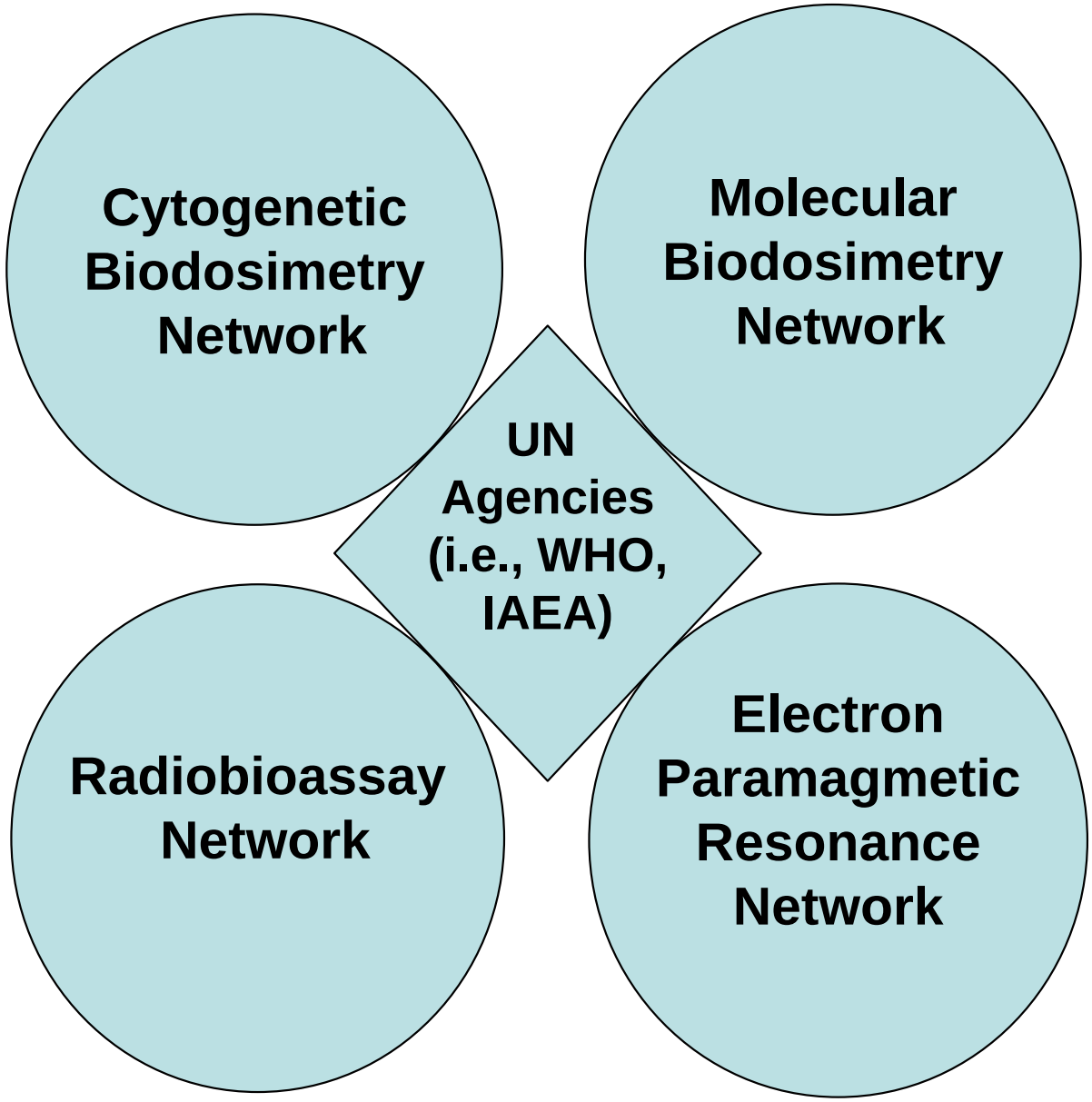


Meeting Report, Radiation Research (in press)

2. Biodosimetry preplanning

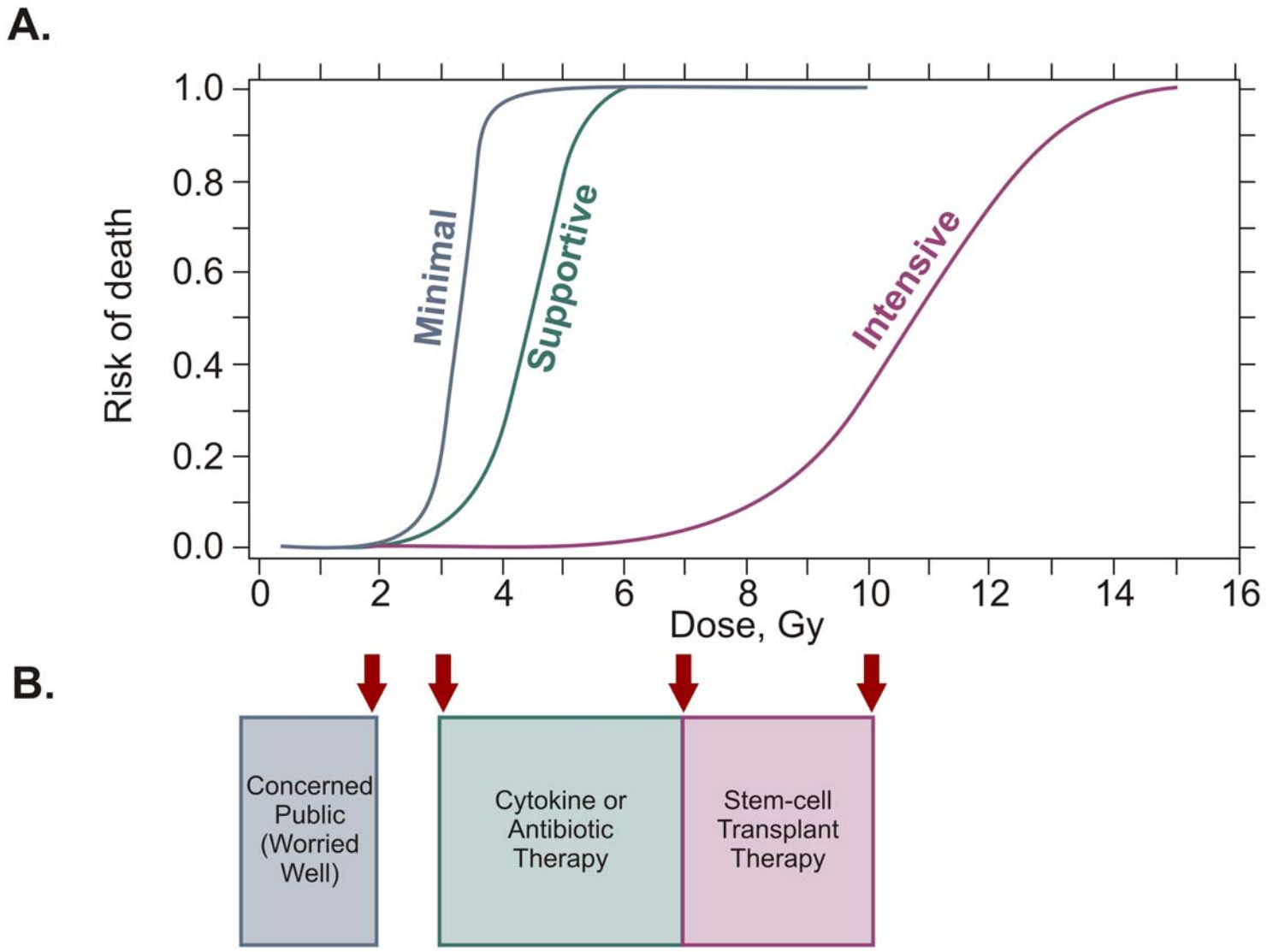
WHO's Network of Expert Reference Laboratories for Dose Assessment

World Health Organization



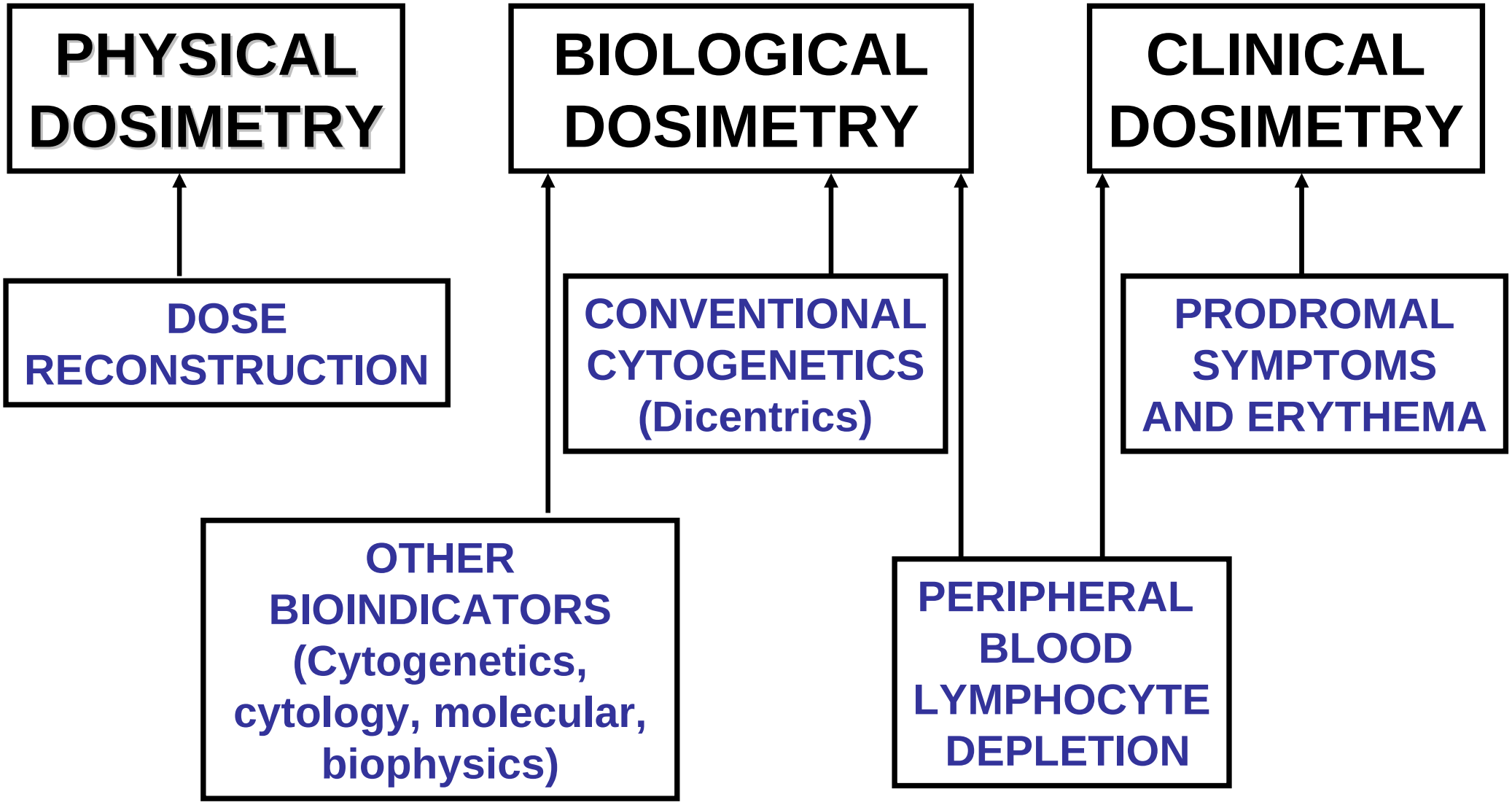
2. Biodosimetry preplanning

Biodosimetry Concept of Operations – Primary Goal

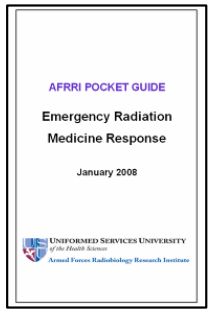


***Waselenko JK, MacVittie TJ, Blakely WF, et al. (2004) *Ann Intern Med*.,140(12):1037–1051.**
Blakely WF, Salter CA, Prasanna PG (2005) Health Physics, 89(5):494-504.

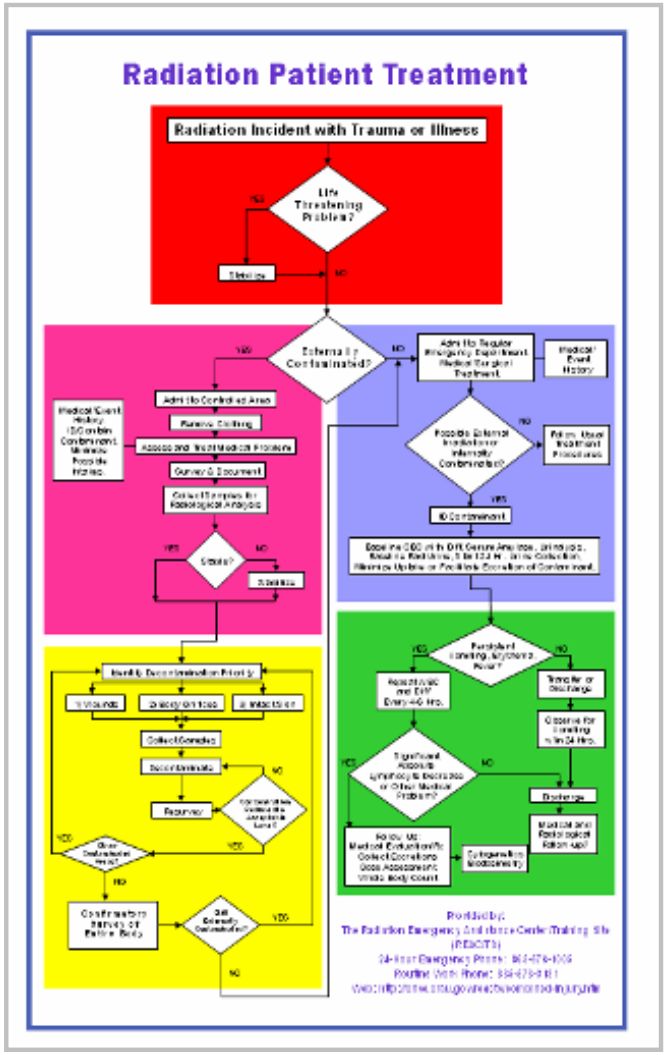
Accidental Exposure Processing



Credits: Modified from materials provided by Voisin (ISPN).



AFRRI Pocket Guide (2008) - NEW

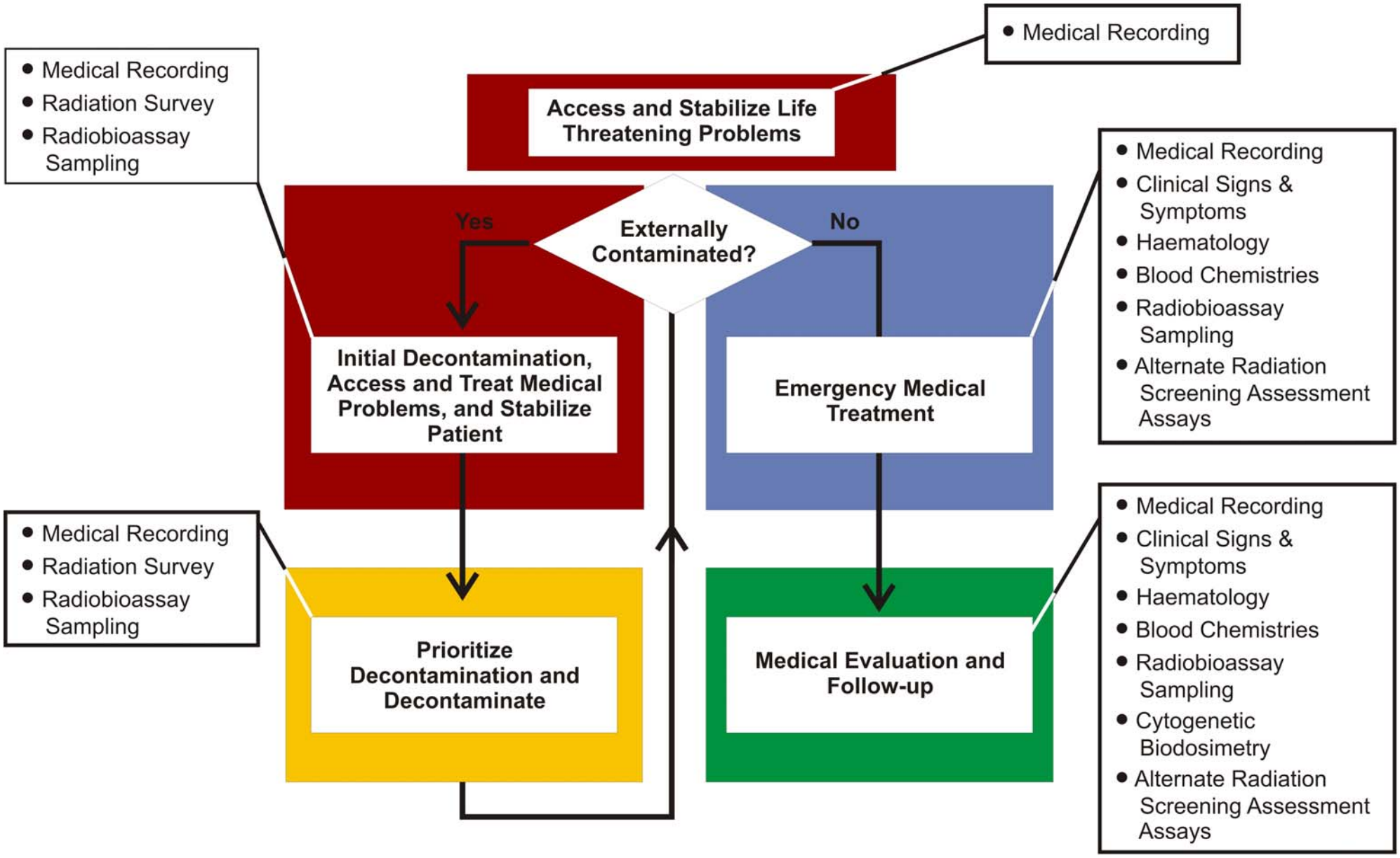


AFRRI website:
http://www.afrri.usuhs.mil

Biodosimetry Concept of Operations:

- Medical recording
- Clinical signs and symptoms
- Radiation surveys and radiobioassays
- Hematology (i.e., CBC with differentials)
- Blood chemistries (i.e., amylase)
- Cytogenetic biodosimetry

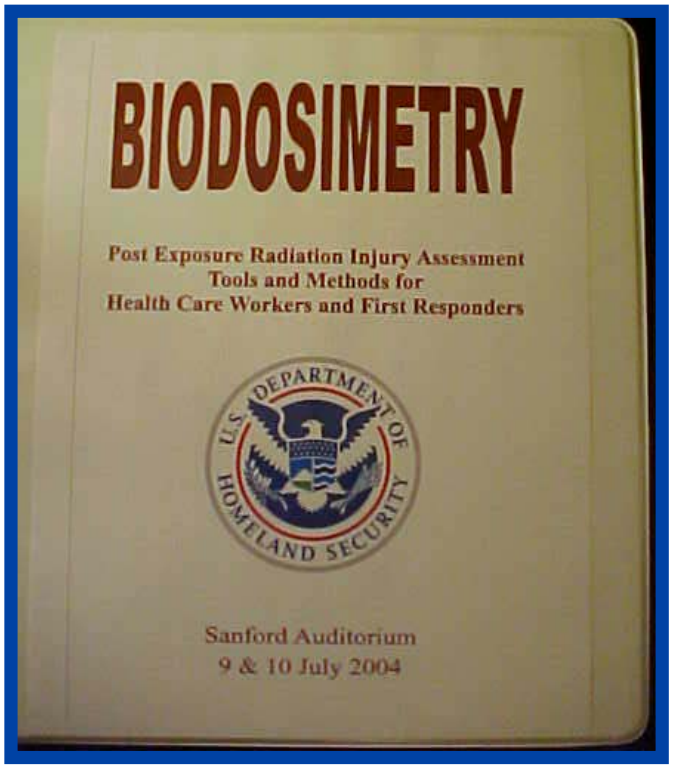
Radiation Patient Treatment Algorithm (Biodosimetry – Concept of Operations)



3. Biodosimetry – concept of operations

Department of Homeland Security 2004 Workshop

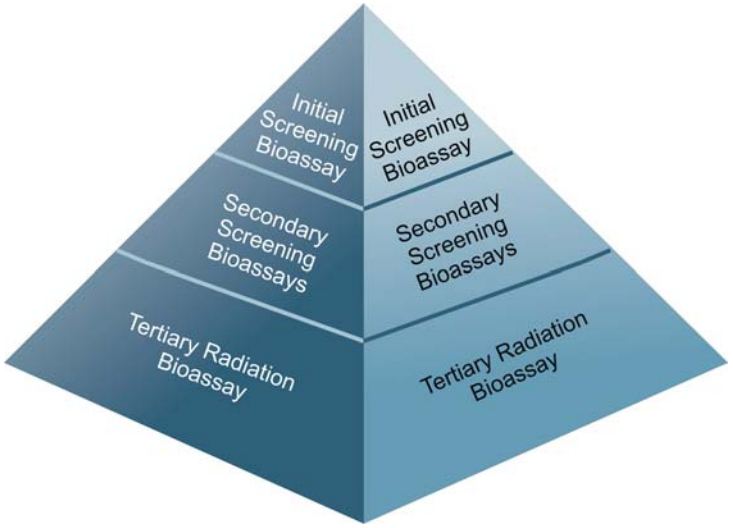
- Post-exposure dose assessment will aid in triage.
- A gap exists in funding lanes for dosimetry devices
- Training & education need to be an integral part of the US response

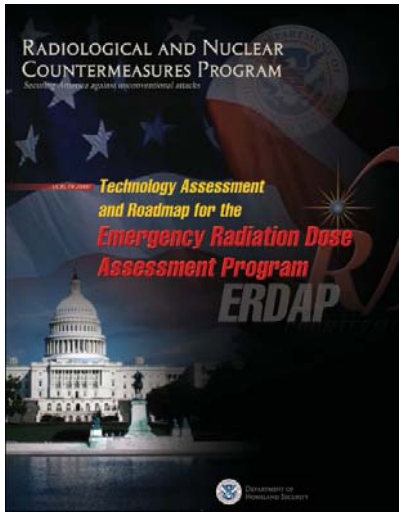


- 5 focus areas + Joint Interagency Working Group → DHS strategy to effectively utilize current assets, identify assessment tools/technologies that can be rapidly fielded, & identify mid- and long-term technologies

Triage is a repetitive process. **It begins at the scene and continues along each step of medical care. Thus, both responders who are first at the scene and acute-care givers at each step of the process must make triage decisions and immediate care decisions in a mass casualty environment. Hospitals will receive self-reporting patients who are self-transports or transported by friends or good-Samaritans**

Joint Interagency Working Group Diagnostic Pyramid Triage Concept





- Hand-held diagnostic device with throughput of 1 assay per 5 minutes or less
- Field-laboratory turnaround time of 24 hours or less
- Hand held field laboratory and reference laboratory radiation dose assessment systems need a detection range 1-8 Gy, with thresholds at 1.5 Gy and 4.5 Gy for triage and 2-3 Gy and 6-7 Gy for treatment decisions for hand-held, field laboratory, and reference laboratory diagnostic dose assessment system.
- Critical need to identify those who do not need immediate medical attention

http://www.afrri.usuhs.mil/outreach/reports.htm

Biodosimetry—General Guidance*

Actions needed in suspected overexposures:

- **Perform measurement and bioassay, if appropriate, to determine radioactivity contamination.**
- **Record physical dosimetry measurements, if available**
- **Observe/record prodromal signs/symptoms and erythema.**
- **Obtain CBC with white blood cell differential immediately, then every six hours for 2 to 3 days, and then twice a day for four days.**
- **Contact qualified laboratory to evaluate performance of chromosome-aberration cytogenetic bioassay, using the "gold standard" dicentric assay for dose assessment.**
- **Consider other opportunistic dosimetry approaches as available.**

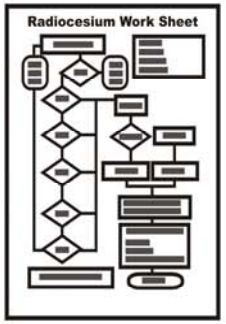
***Waselenko JK, MacVittie TJ, Blakely WF, et al. (2004) *Ann Intern Med*.,140(12):1037–1051.**
Blakely WF, Salter CA, Prasanna PG (2005) Health Physics, 89(5):494-504.

4. Early-response multiple parameter biodosimetry

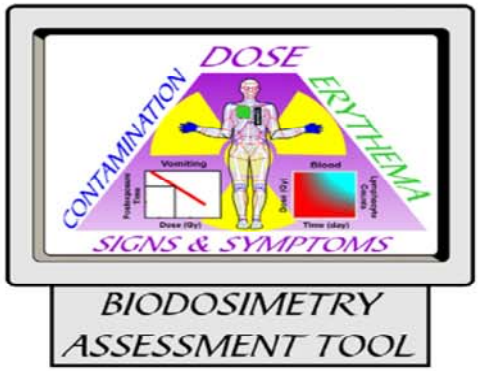
Biodosimetry Tools Supporting Medical Recording

www.afrri.usuhs.mil/outreach/biodostools.htm

Medical Recording Forms



Software Program for Collection of Radiation Exposure Medical Data



First-Responder Radiological Assessment Triage (FRAT)

Expert panel weighted triage dose based on currently available biodosimetric indices

Outreach Distribution

Military Medicine Operations CDROM

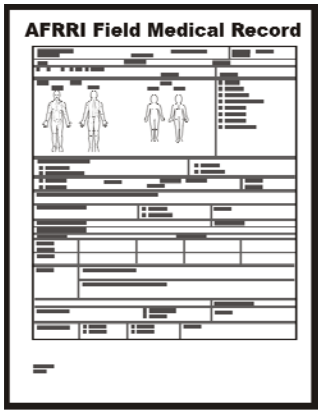
4. Early-response multiple parameter biodosimetry

Medical Recording Forms

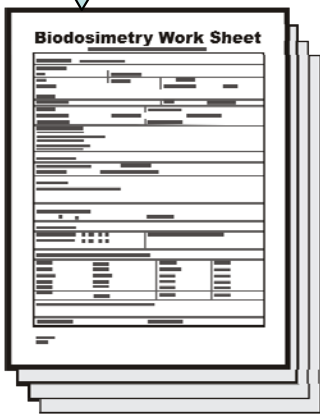
AFRRI Adult/Pediatric Field Medical Record:
This medical record provides a convenient one-page form for gathering emergency medical information in the field. It is applicable to both adult and pediatric cases.

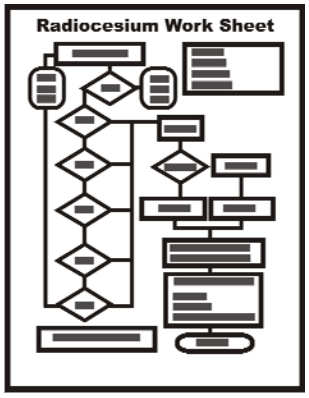
AFRRI Biodosimetry Worksheet:
This data entry worksheet, recently expanded from four to six pages, provides a place for recording the facts about a case of radiation exposure, including the source and type of radiation, the extent of exposure, and the nature of the resulting injuries. Applicable to both adult and pediatric cases.

Prussian blue work sheet: AFRRI Form 335 describes the initial assessment and treatment of casualties from a radiation dispersal device (RDD) event that involves the dispersal of radioactive cesium or thorium.



Updated worksheet includes the METREPOL ARS severity response scoring system





AFRRI website: www.afrri.usuhs.mil

4. Early-response multiple parameter biodosimetry

Medical Treatment Protocols (METREPOL) for Radiation Accident Victims

SYMPTOMS

N
- Nausea
- Vomiting
- Anorexia
- Fatigue syndrome
- Fever
- Headache
- Hypotension
- Neurological deficits
- Cognitive deficits

H
- Lymphocytes changes
- Granulocyte changes
- Thrombocyte changes
- Blood loss
- Infection

C
- Erythema
- Sensation/itching
- Swelling/Edema
- Blistering
- Desquamation
- Ulcer/Necrosis
- Hair loss
- Onycholysis

G
- Diarrhea
- Abdominal cramps/pain

GRADING (organ specific)

N_i H_i C_i G_i

GRADING CODE

$N_i H_i C_i G_i$

RESPONSE CATEGORY

$RC = ?_{xd}$

N = Neurovascular system
H = Hematopoietic system
C = Cutaneous system
G = Gastrointestinal system
i = Degree of severity 1-4
xd = Time point (x) at which RC was measured in days (d) after beginning of exposure

EXAMPLE:

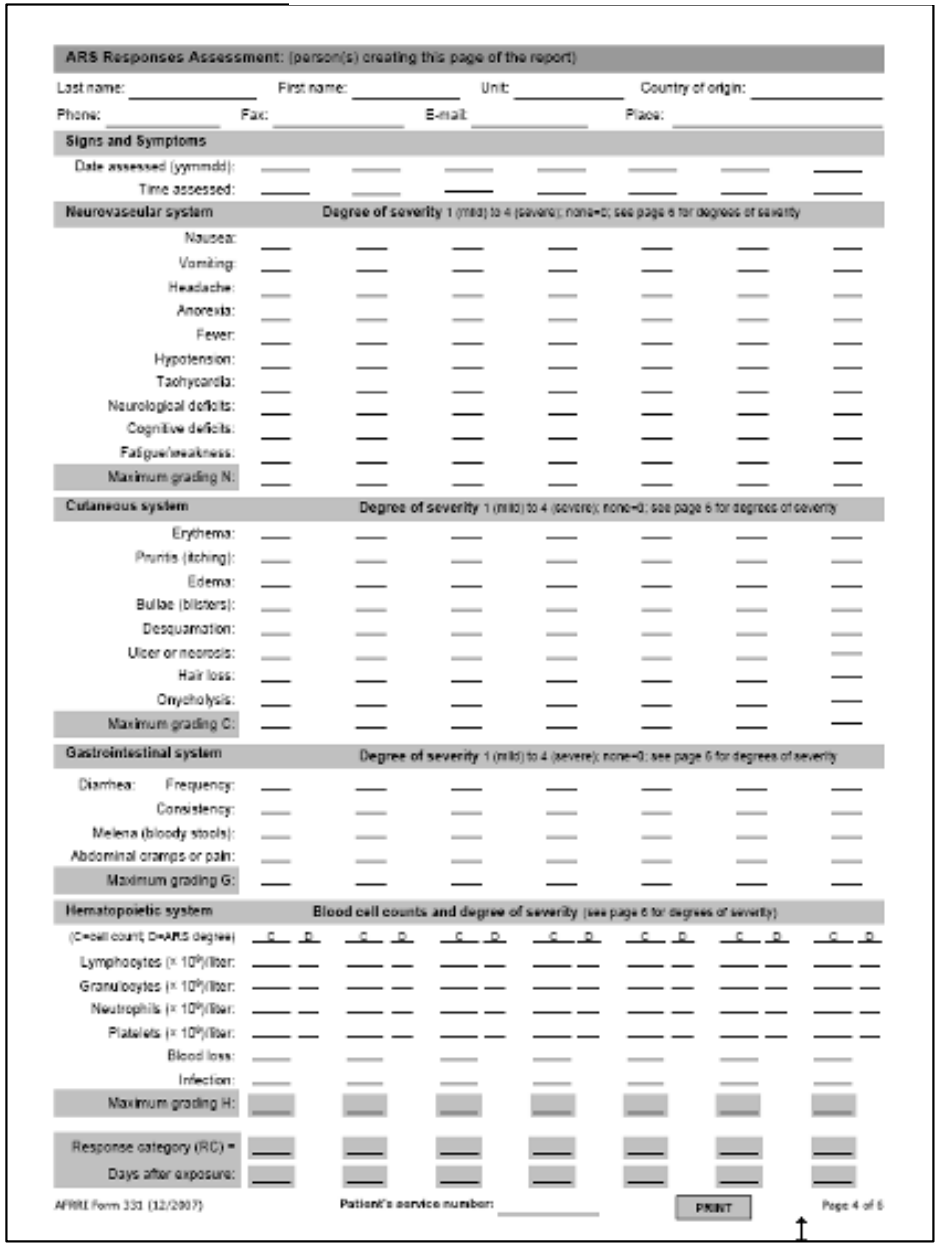
N2 → $N_2H_3C_1G_2$ → $RC = 3_{2d}$

- Capital letter for the organ system, e.g. neurovascular system
- Degree of severity to describe the extent of damage
- A RC equal to 3 was determined on the second day after exposure

Adapted from Medical Management of Radiation Accident, Manual on the Acute Radiation Syndromes, The British Institute of Radiobiology, 2001

AFRRI Biodosimetry Worksheet

(Medical Record of Radiation Dose, Contamination, and Acute Radiation Sickness Response)



ARS Responses Assessment: (person(s) creating this page of the report)

Last name: First name: Unit: Country of origin:

Phone: Fax: E-mail: Place:

Signs and Symptoms

Date assessed (yymmdd):
Time assessed:

Neurovascular system — Degree of severity 1 (mild) to 4 (severe); none=0; see page 6 for degrees of severity

Nausea:
Vomiting:
Headache:
Anorexia:
Fever:
Hypotension:
Tachycardia:
Neurological deficits:
Cognitive deficits:
Fatigue/weakness:
Maximum grading N:

Cutaneous system — Degree of severity 1 (mild) to 4 (severe); none=0; see page 6 for degrees of severity

Erythema:
Pruritis (itching):
Edema:
Bullae (blisters):
Desquamation:
Ulcer or necrosis:
Hair loss:
Onycholysis:
Maximum grading C:

Gastrointestinal system — Degree of severity 1 (mild) to 4 (severe); none=0; see page 6 for degrees of severity

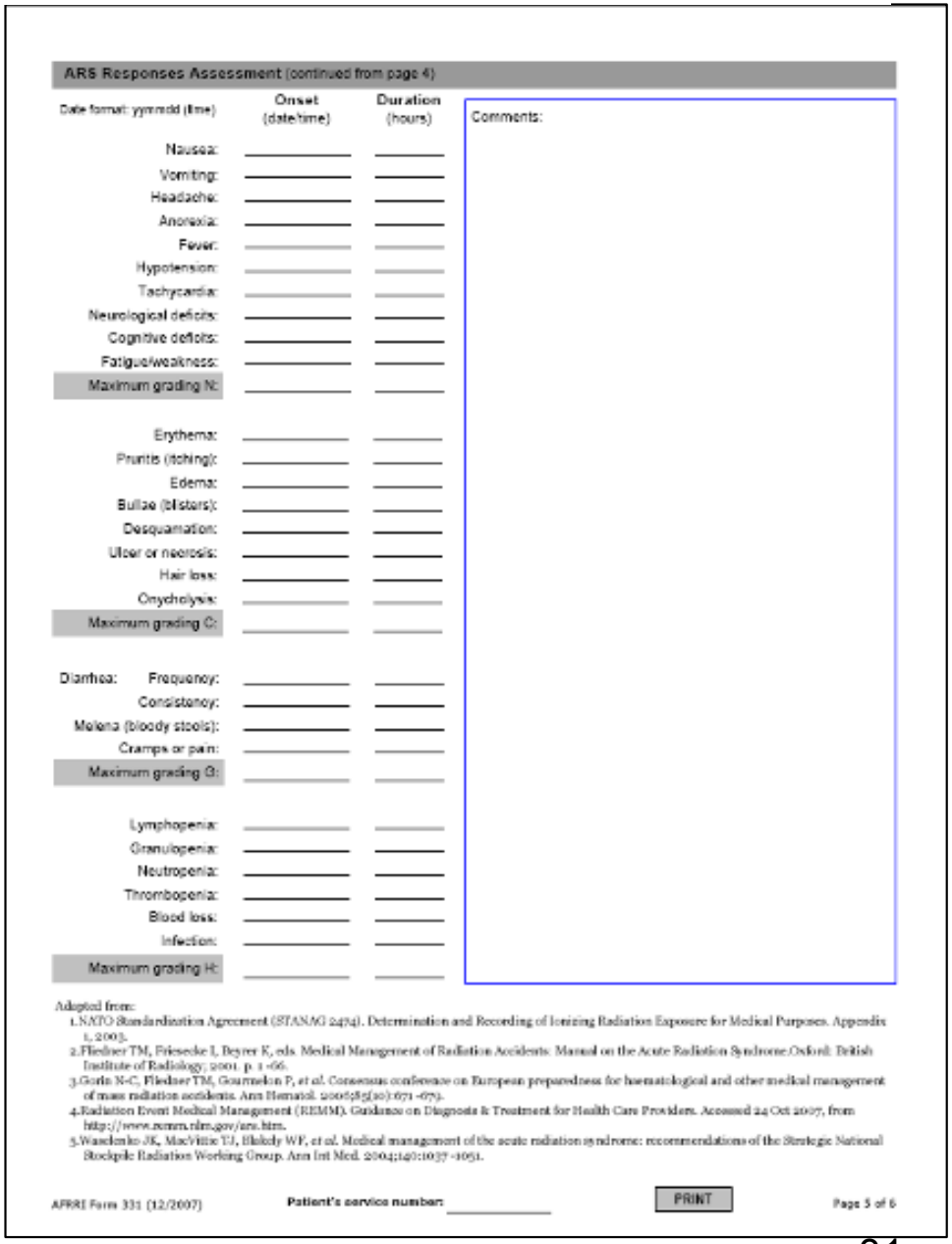
Diarrhea: Frequency:
Consistency:
Melena (bloody stools):
Abdominal cramps or pain:
Maximum grading G:

Hematopoietic system — Blood cell counts and degree of severity (see page 6 for degrees of severity)

(C=cell count; D=ARS degree)
Lymphocytes (× 10^9)/liter:
Granulocytes (× 10^9)/liter:
Neutrophils (× 10^9)/liter:
Platelets (× 10^9)/liter:
Blood loss:
Infection:
Maximum grading H:

Response category (RC) =
Days after exposure:

AFRRI Form 331 (12/2007) Patient's service number: PRINT Page 4 of 6



ARS Responses Assessment (continued from page 4)

Date format: yymmdd (time)	Onset (date/time)	Duration (hours)
Nausea:		
Vomiting:		
Headache:		
Anorexia:		
Fever:		
Hypotension:		
Tachycardia:		
Neurological deficits:		
Cognitive deficits:		
Fatigue/weakness:		
Maximum grading N:		
Erythema:		
Pruritis (itching):		
Edema:		
Bullae (blisters):		
Desquamation:		
Ulcer or necrosis:		
Hair loss:		
Onycholysis:		
Maximum grading C:		
Diarrhea: Frequency:		
Consistency:		
Melena (bloody stools):		
Cramps or pain:		
Maximum grading G:		
Lymphopenia:		
Granulopenia:		
Neutropenia:		
Thrombopenia:		
Blood loss:		
Infection:		
Maximum grading H:		

Comments:

Adapted from:

1.NATO Standardization Agreement (STANAG 2474). Determination and Recording of Ionizing Radiation Exposure for Medical Purposes. Appendix 1, 2003.
2.Fliedner TM, Friesecke I, Beyrer K, eds. Medical Management of Radiation Accidents: Manual on the Acute Radiation Syndrome.Oxford: British Institute of Radiology; 2001. p. 1-66.
3.Gorin N-C, Fliedner TM, Gourmelon P, et al. Consensus conference on European preparedness for haematological and other medical management of mass radiation accidents. Ann Hematol. 2006;85(10):671-673.
4.Radiation Event Medical Management (REMM). Guidance on Diagnosis & Treatment for Health Care Providers. Accessed 24 Oct 2007, from http://www.remm.nlm.gov/are.htm.
5.Waselenko JK, MacVittie TJ, Blakely WF, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann Int Med. 2004;140:1037-1051.

AFRRI Form 331 (12/2007) Patient's service number: PRINT Page 5 of 6

4. Early-response multiple parameter biodosimetry

AFRRI Biodosimetry Worksheet

(Medical Record of Radiation Dose, Contamination, and Acute Radiation Sickness Response)

Modified original METREPOL severity score for hematology kinetics

APPENDIX

Grading System for Response of Neurovascular, Gastrointestinal, Cutaneous, and Hematopoietic Systems

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
Neurovascular system				
Nausea:	Mild	Moderate	Intense	Excruciating
Vomiting:	Occasional (one per d)	Intermittent (2–5 times per d)	Persistent (6–10 times per d)	Refractory (> 10 times per d)
Headache:	Minimal	Moderate	Intense	Excruciating
Anorexia:	Able to eat & drink	Intake decreased	Intake minimal	Parenteral nutrition
Fever:	< 38°C	38–40°C	> 40°C for < 24 h	> 40°C for > 24 h
Hypotension:	Heart rate >100 beats/m; blood pressure > 100/70 mm Hg	Blood pressure < 100/70 mm Hg	Blood pressure < 90/60 mm Hg: transient	Blood pressure < 80/? mm Hg: persistent
Neurological deficits:	Barely detectable	Easily detectable	Prominent	Life-threatening, loss of consciousness
Cognitive deficits:	Minor loss	Moderate loss	Major impairment	Complete impairment
Fatigue/weakness:	Able to work	Interferes with work or normal activity	Needs assistance for self care	Prevents daily activities
Cutaneous system				
Erythema:	Minimal, transient	Moderate (< 10% body surface area)	Marked (10–40% body surface area)	Severe (> 40% body surface area)
Pruritis (itching):	Sensation of itching	Slight and intermitten pain	Moderate and persistent pain	Severe and persistent pain
Edema:	Persistent, asymptomatic	Symptomatic, tension	Secondary dysfunction	Total dysfunction
Blistering:	Rare, sterile fluid	Rare, hemorrhage	Bullae, sterile fluid	Bullae, hemorrhage
Desquamation:	Absent	Patchy dry	Patchy moist	Confluent moist
Ulcer or necrosis:	Epidermal only	Dermal	Subcutaneous	Muscle/bone involvement
Hair loss:	Thinning, not striking	Patch, visible	Complete, reversible	Complete, irreversible
Onycholysis:	Absent	Partial	Partial	Complete
Gastrointestinal system				
Diarrhea:				
Frequency, stools/d:	2–3	4–6	7–9	≥ 10; refractory diarrhea
Consistency:	Bulky	Loose	Very loose	Watery
Melena (bloody stools):	Occult	Intermittent	Persistent	Persistent; large amount
Abdominal cramps/pain:	Minimal	Moderate	Intense	Excruciating
Hematopoietic system				
Lymphocyte changes: (reference value, 1.4–3.5 × 10^9 cells/L)	1–2d: ≥ 1.5	1–2d: 1–1.5	1–2d: 0.5–1	1–2d: < 0.5
	3–7d: ≥ 1	3–7d: 0.5–1	3–7d: 0.1–0.5	3–7d: < 0.1
Granulocyte changes: (reference value, 4–9 × 10^9 cells/L)	1–2d: ≥ 2	1–2d: 4–6; mild	1–2d: 6–10; moderate	1–2d: > 10; marked
	3–7d: ≥ 2	3–7d: > 2	3–7d: > 5	3–7d: > 5
Thrombocyte (platelets) changes: (reference value, 140–400 × 10^9 cells/L)	1–2d: ≥ 100	1–2d: 50–100	1–2d: 50–100	1–2d: 50–100
	3–7d: ≥ 100	3–7d: 50–100	3–7d: 20–50	3–7d: < 20
Blood loss:	Petechiae, easy bruising, normal hemoglobin level	Mild blood loss with < 10% decrease in hemoglobin level	Gross blood loss with 10%–20% decrease in hemoglobin level	Spontaneous bleeding or blood loss with > 20% decrease in hemoglobin level
Infection:	Local, no antibiotic therapy required	Local; only local antibiotic therapy required	Systemic; p.o. antibiotic treatment sufficient	Sepsis; i.v. antibiotics necessary

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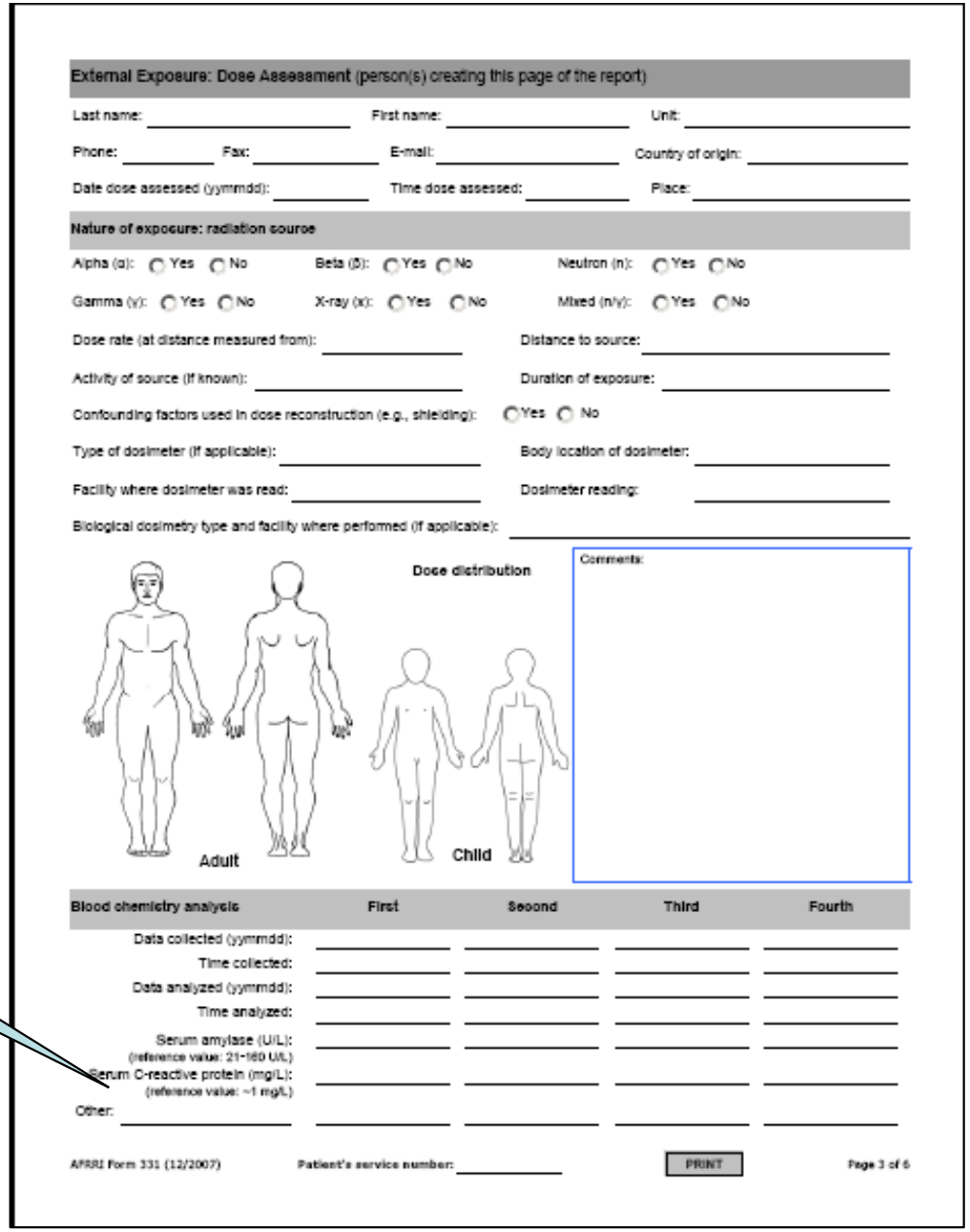
4. Early-response multiple parameter biodosimetry

AFRRI Biodosimetry Worksheet

(Medical Record of Radiation Dose, Contamination, and Acute Radiation Sickness Response)



External Exposure: Dose Assessment (person(s) creating this page of the report)

Last name: First name: Unit:

Phone: Fax: E-mail: Country of origin:

Date dose assessed (yymmdd): Time dose assessed: Place:

Nature of exposure: radiation source

Alpha (α): Yes No Beta (β): Yes No Neutron (n): Yes No

Gamma (γ): Yes No X-ray (x): Yes No Mixed (n/γ): Yes No

Dose rate (at distance measured from): Distance to source:

Activity of source (if known): Duration of exposure:

Confounding factors used in dose reconstruction (e.g., shielding): Yes No

Type of dosimeter (if applicable): Body location of dosimeter:

Facility where dosimeter was read: Dosimeter reading:

Biological dosimetry type and facility where performed (if applicable):

Dose distribution

Adult

Child

Comments:

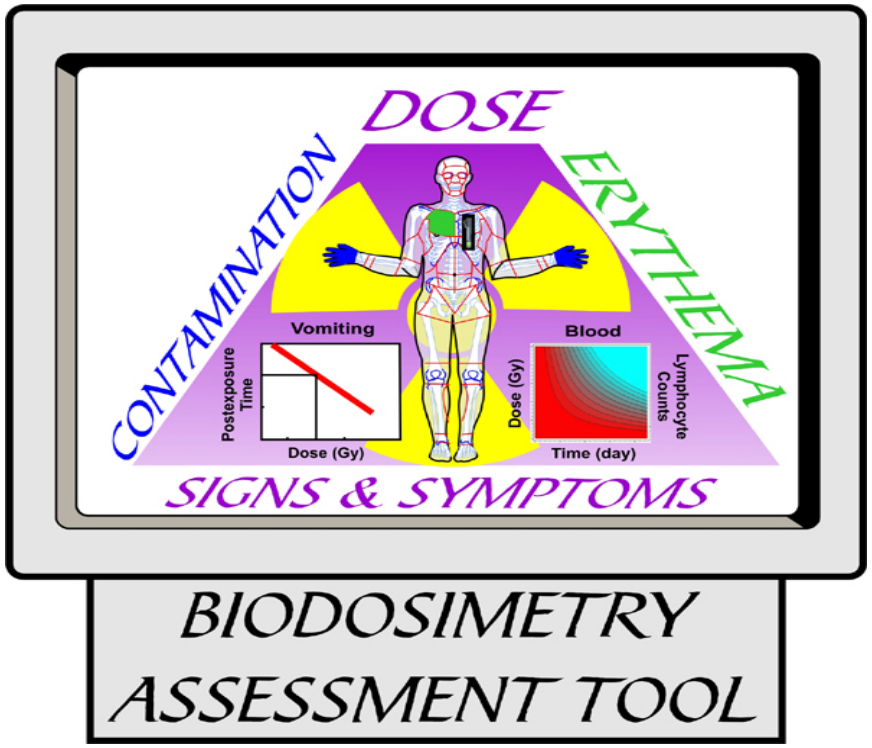
Blood chemistry analysis	First	Second	Third	Fourth
Data collected (yymmdd):				
Time collected:				
Data analyzed (yymmdd):				
Time analyzed:				
Serum amylase (U/L): (reference value: 21-160 U/L)				
Serum C-reactive protein (mg/L): (reference value: ~1 mg/L)				
Other:				

AFRRI Form 331 (12/2007) Patient's service number: PRINT Page 3 of 6

Serum amylase
C-reactive protein

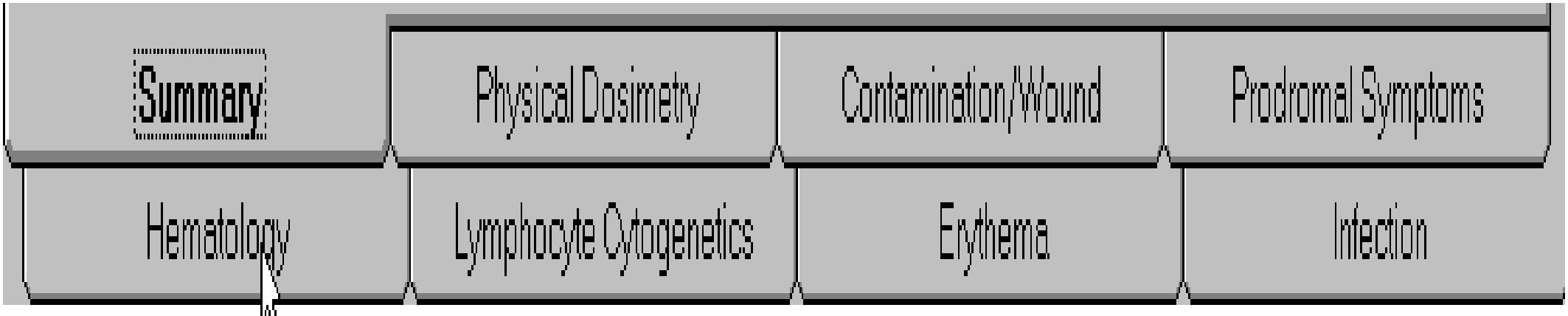
4. Early-response multiple parameter biodosimetry

Software Program for Collection of Radiation Exposure Medical Data

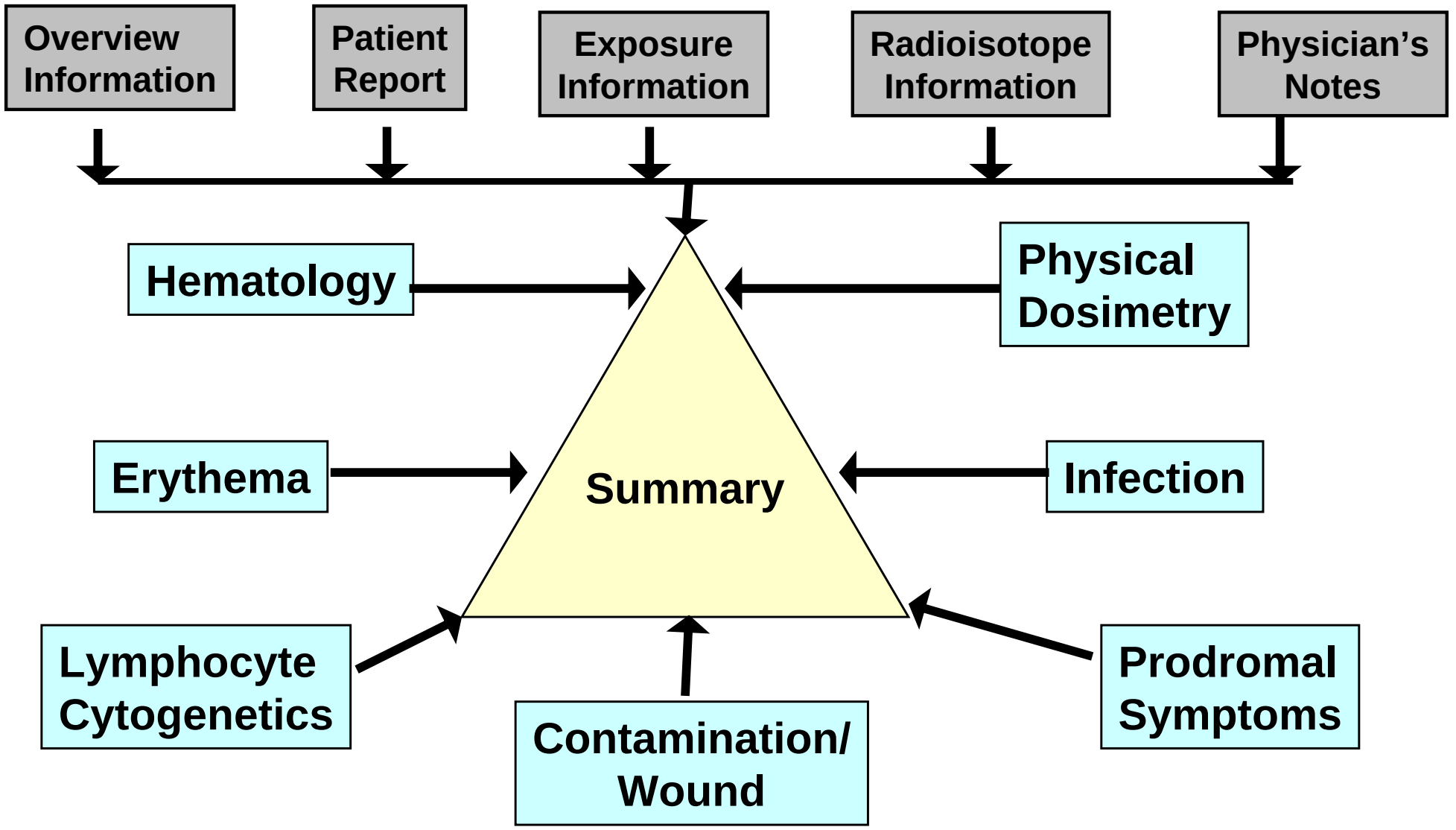


www.afrri.usuhs.mil

- **Primarily permits recording of relevant indices of radiation injury.**
- **Interprets dose-related diagnostic signs and symptoms (i.e., lymphocyte cell counts, times onset of emesis).**



Program Schematic: BAT Application

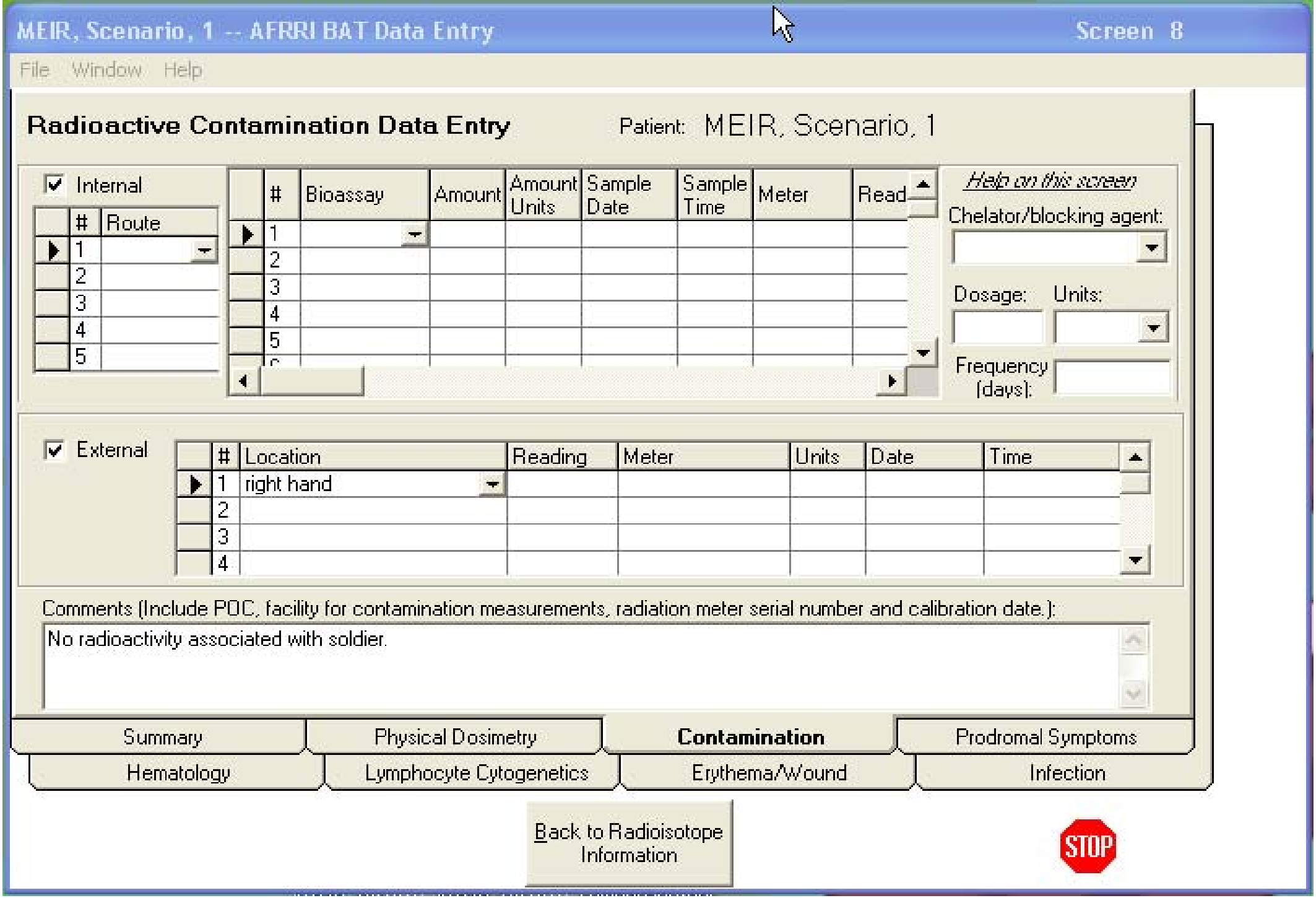


4. Early-response multiple parameter biodosimetry

General Guidance – Suspected Internal Radioactivity Contamination*

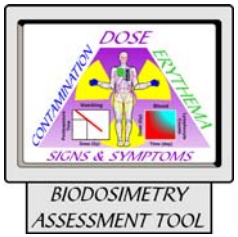
- **Radioactivity decontamination to minimize local dose to potential wound site**
- **Metallic (or other) fragment sample collection for isotope identification**
- **Biological sample collection (e.g., urinalysis, fecal, wound, swipes from body orifices) for determination of committed dose**

***Recommendations of the Biodosimetry and Devices Subpanel of the Radiological / Nuclear Threat Countermeasures (RNTC) Working Group for the Office of Science and Technology Policy – Homeland Security Council.**



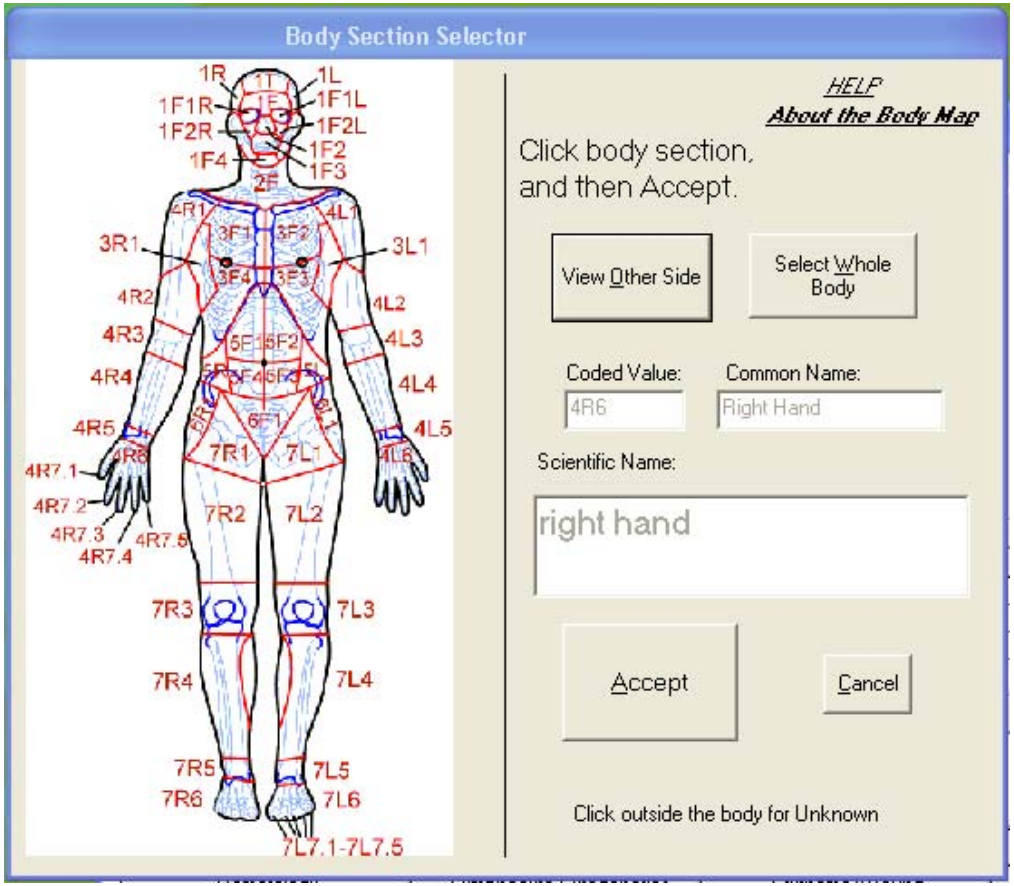
4. Early-response multiple parameter biodosimetry

Data for Estimation of Internal Dose



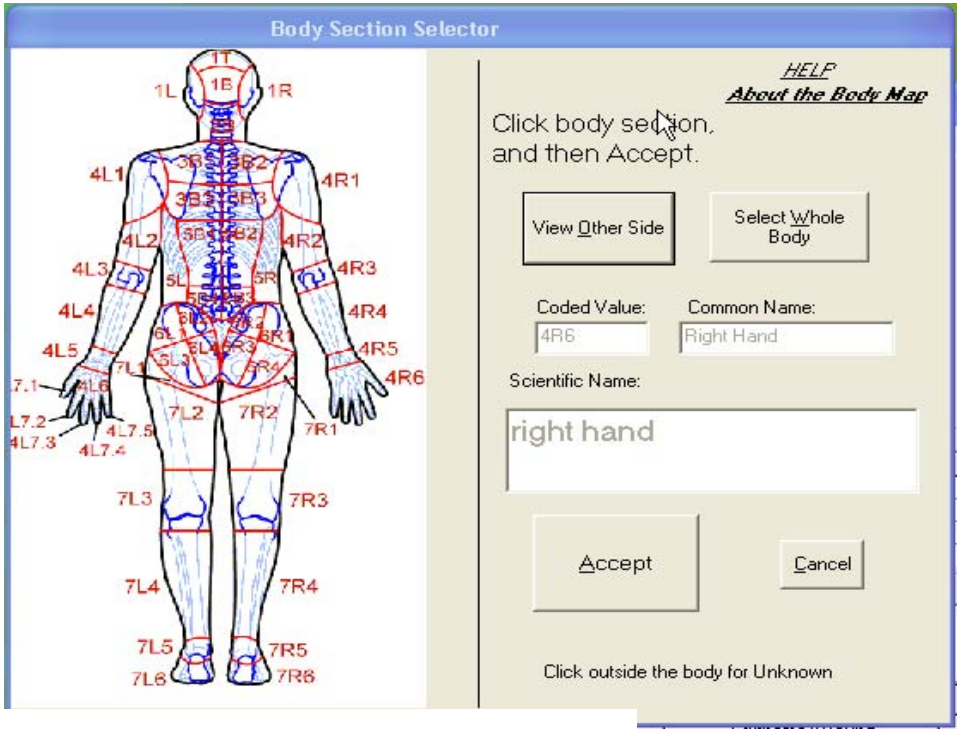
- **Internal contamination**
  - Isotope
  - Mode of internalization
  - Assays: radon/lung, nasal swipes,
  - Urine samples, fecal samples, others
  - Time course measurements
- **Wounds/ contaminated wounds**
  - Type: abrasion, burn, laceration, puncture
  - Location: anatomical figure for easy entry
  - Time course measurements
- **External (non-wound) contamination**
  - Whole-body and partial-body counting
  - Meter pick list
  - Reading entry
  - Units with Sievert - Gray conversion
  - Location: anatomical figure for easy entry

Anatomical Location



- Data entry screens that use the Body Section Selector tool

- PHYSICAL DOSIMETRY
  - Location worn on body
- ERYTHEMA/WOUND
  - Location of erythema
  - Location of wound
- RADIOACTIVE CONTAMINATION
  - External contamination location



BAT user clicks on affected region, which is automatically entered in "location" section of appropriate data entry table.

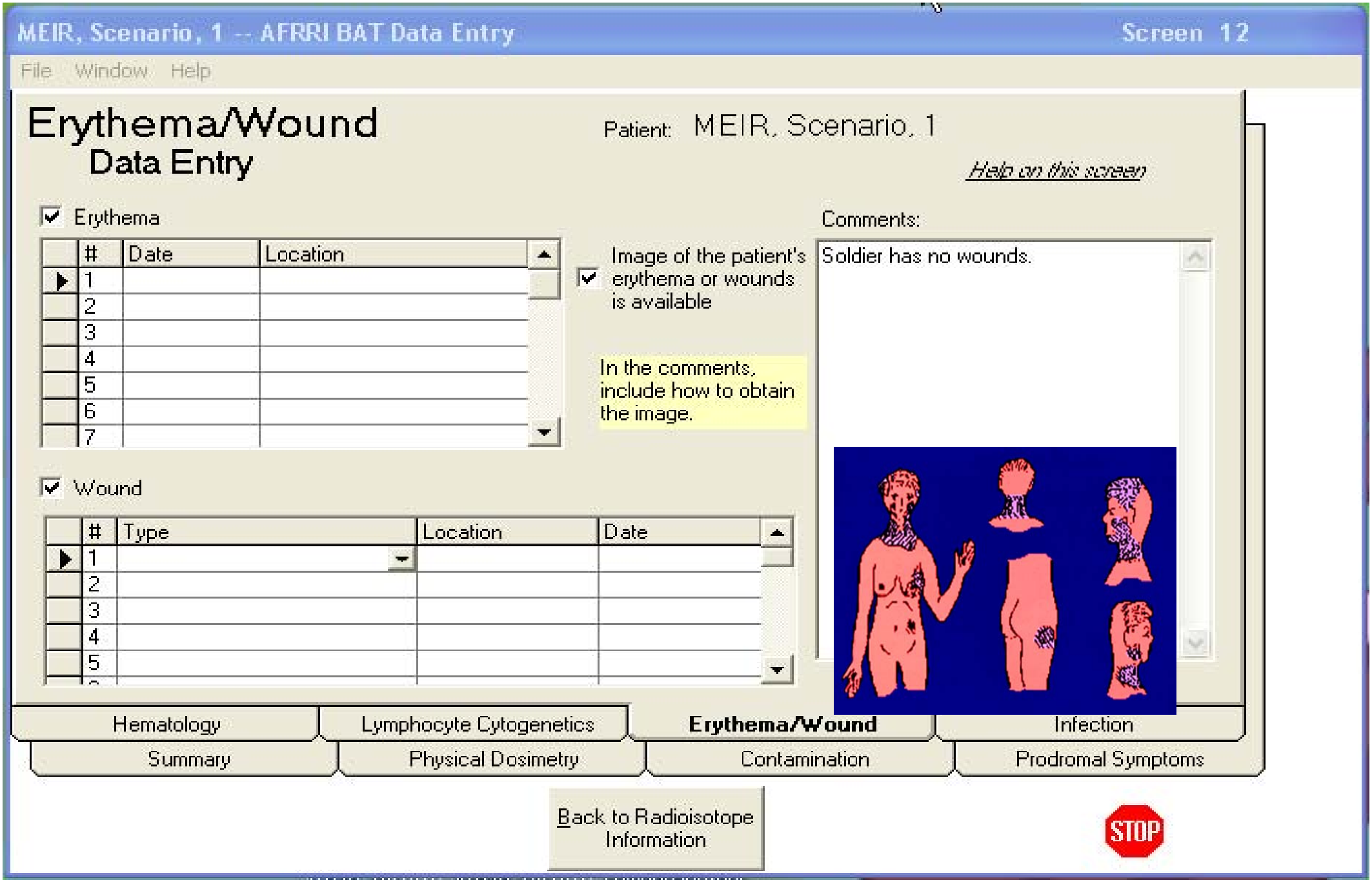
4. Early-response multiple parameter biodosimetry

Bioassay for Internal Contamination of Radioactivity

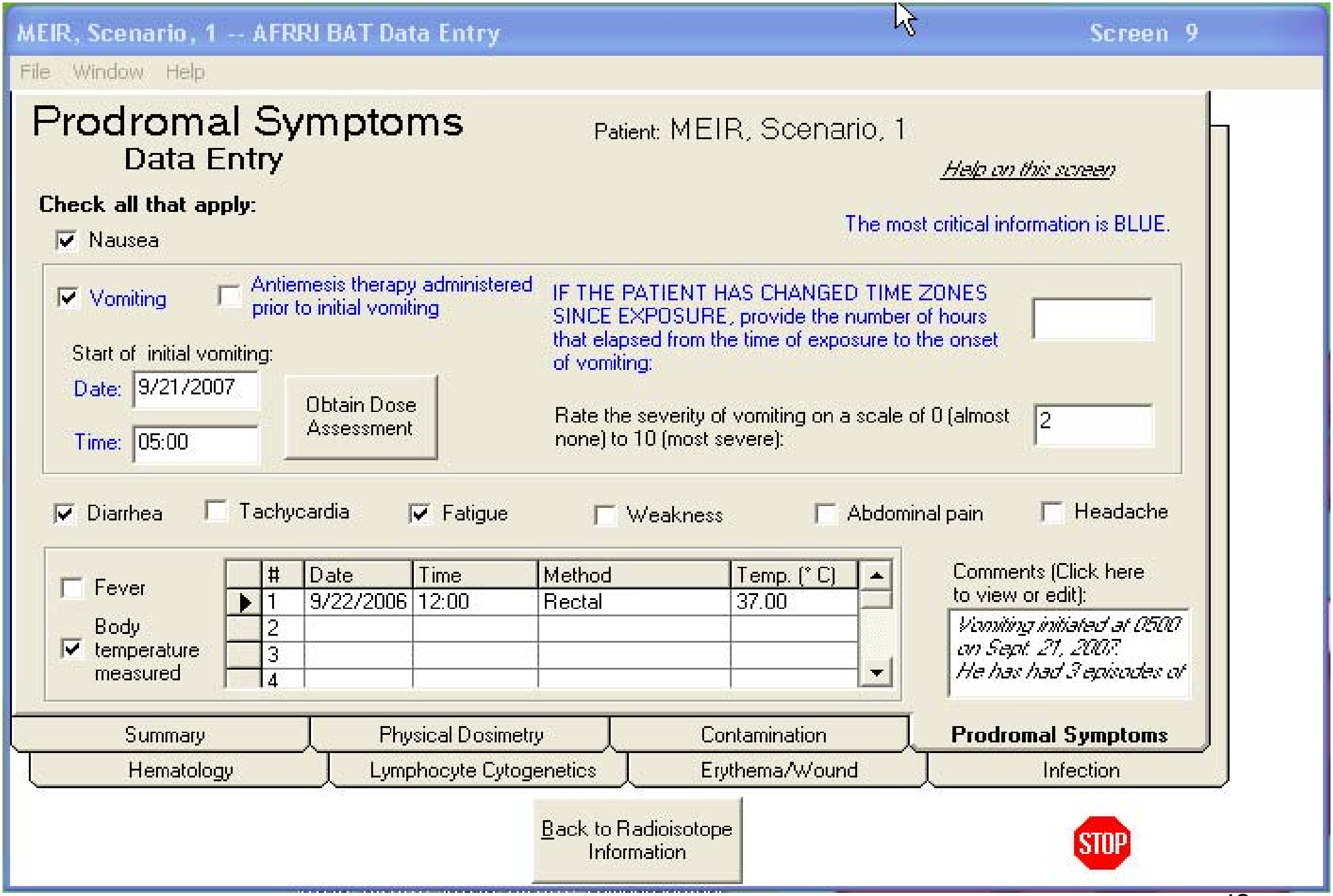
Laboratory capability for medical facility/hospital satellite reception center, field hospital, or medical response teams

- Biodosimetry and Devices Subpanel* of the RNTC Working Group recommended critical supply items be stockpiled and available to provide appropriate medical response to situations involving mass radiological casualties and also recommended research efforts to enhance automation of sample processing by radioactivity counting laboratories.
- Deployable bioassay sampling is part of the “Medical Support Team” for IAEA’s Emergency Response Network now known as RANET.

***Dr. James Smith was a Subpanel participant and provided significant contributions in this area.**



4. Early-response multiple parameter biodosimetry



4. Early-response multiple parameter biodosimetry

Onset of Vomiting

BIODOSIMETRY ASSESSMENT TOOL

Vomiting

Antiemesis therapy administered prior to initial vomiting

Start of initial vomiting:

Date: 9/21/2007

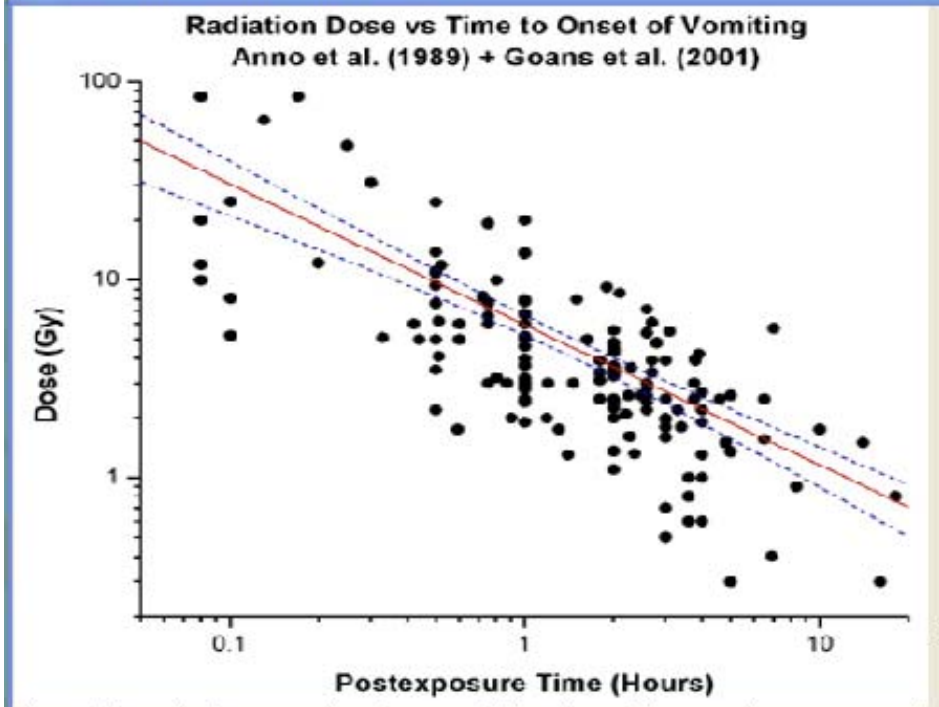
Time: 05:00

Obtain Dose Assessment

IF THE PATIENT HAS CHANGED TIME ZONES SINCE EXPOSURE, provide the number of hours that elapsed from the time of exposure to the onset of vomiting:

Rate the severity of vomiting on a scale of 0 (almost none) to 10 (most severe): 2

Obtain Dose Estimate from Emesis



Print this form

Time from exposure to onset of vomiting: 7.00 Hours

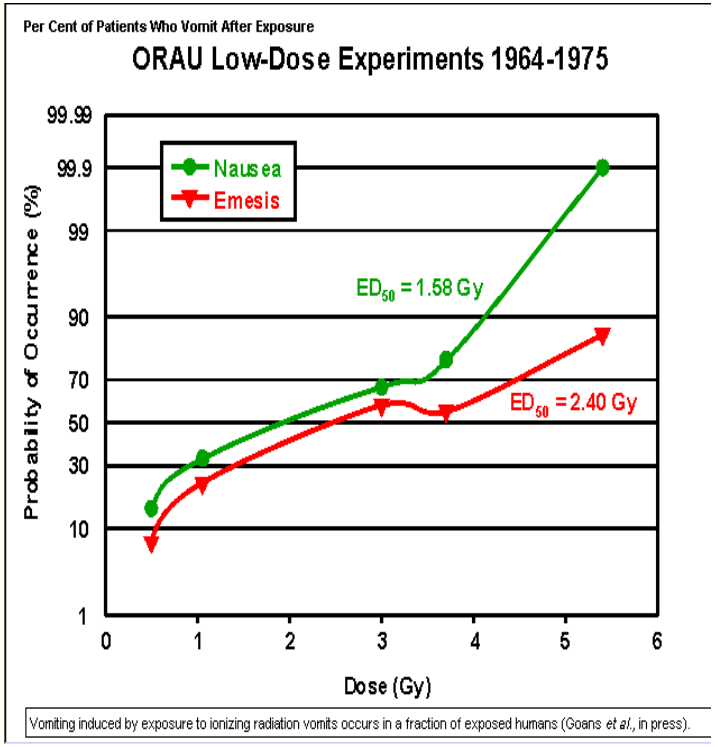
Estimated dose at time of exposure: 1.5 Gray (Gy)

95% CL (Gy): 1.1-1.9

Patient: MEIR, Scenario, 1

Anno, G.H., et al., Symptomatology of acute radiation effects in humans after exposure to doses of 0.5-30 Gy (Health Physics, Vol 56(6): 821-838, 1989). Dose rates ranged from very high (accident cases) down to 0.3 Gy/min (radiotherapy patients). Goans, RE, Clinical care of the radiation accident patient: patient presentation, assessment, and initial diagnosis (Found in: The Medical Basis for Radiation Accident Preparedness: The Clinical Care of Victim, Proceedings of the 4th International REAC/TS, Orlando, FL, March, 2001, Editors: Robert C. Ricks, Mary Ellen Berger, and Frederick M. Ohara, Jr., The Parthenon Publishing, Boca Raton, FL, 2001.). In general, midline doses are quoted. Confidence limits (dashed blue line) represent one SE from the fitted line (solid red).

Return to Data Entry



4. Early-response multiple parameter biodosimetry

Forward Deployable Military Labs and Capability

DTRA/Air Force Fly-Away

- **Physical dosimetry (TLD)**
- **Blood cell counting (AFRRI)**
- **BAT software (AFRRI)**
- **Internal dosimetry, radioactivity counting**

Defense Threat Reduction Agency (DTRA)

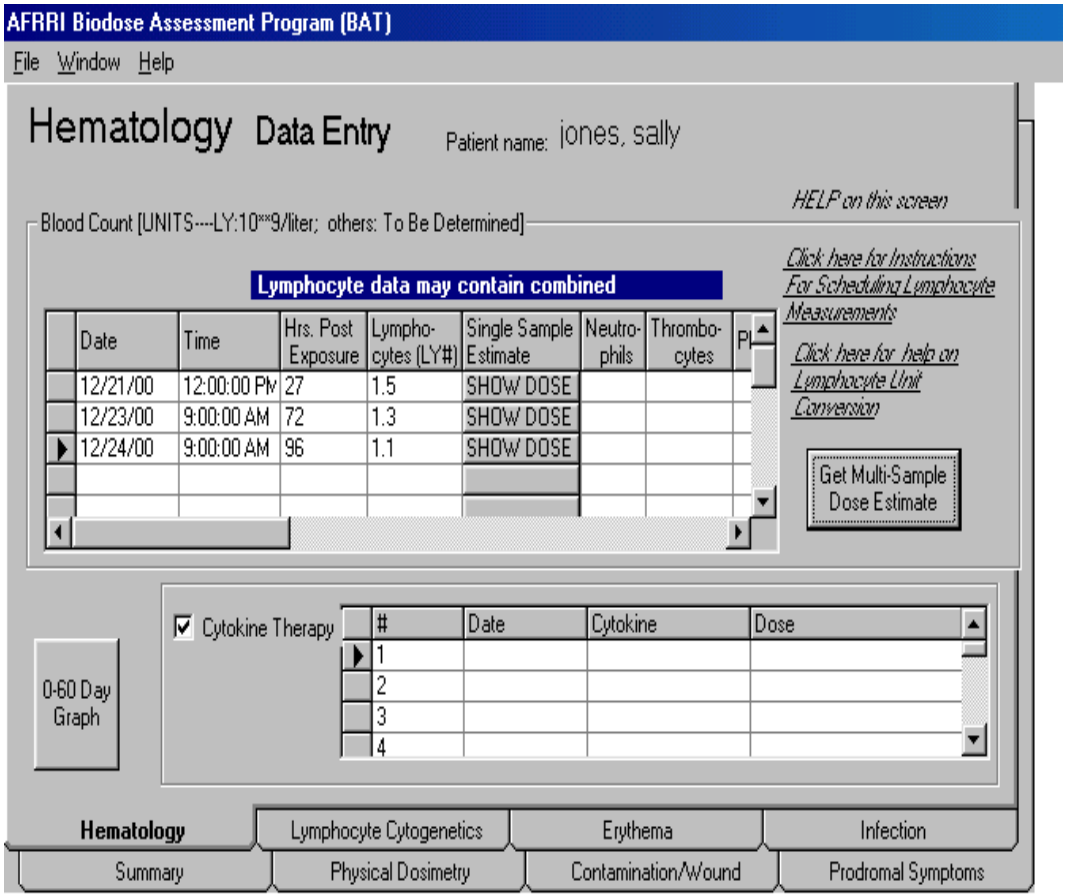
Deployable Hematology

Laboratory capability for medical facility/hospital satellite reception center, field hospital, or medical response teams

- AFRRI provided equipment and supply list for Department of Defense applications
- Biodosimetry and Devices Subpanel* of the Radiological / Nuclear Threat Countermeasures (RNTC) Working Group for the Office of Science and Technology Policy – Homeland Security Council recommended that similar supply and equipment items be stockpiled and available to provide appropriate medical response to situations involving mass radiological casualties
- Deployable hematology capability is part of the "Medical Support Team" for IAEA's Emergency Response Network now known as RANET

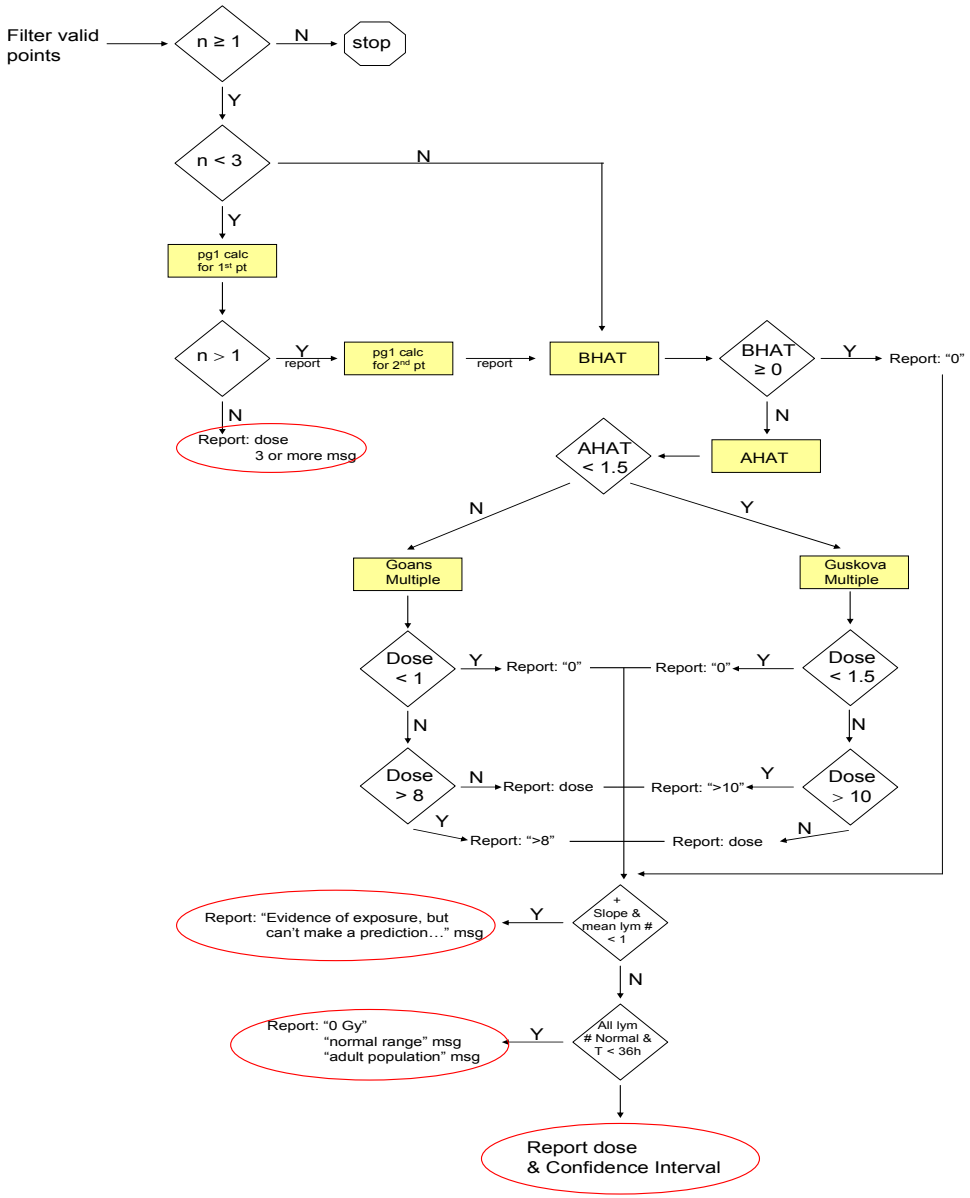
***Subpanel co-chaired by Drs. Robert C. Ricks and W.F. Blakely**

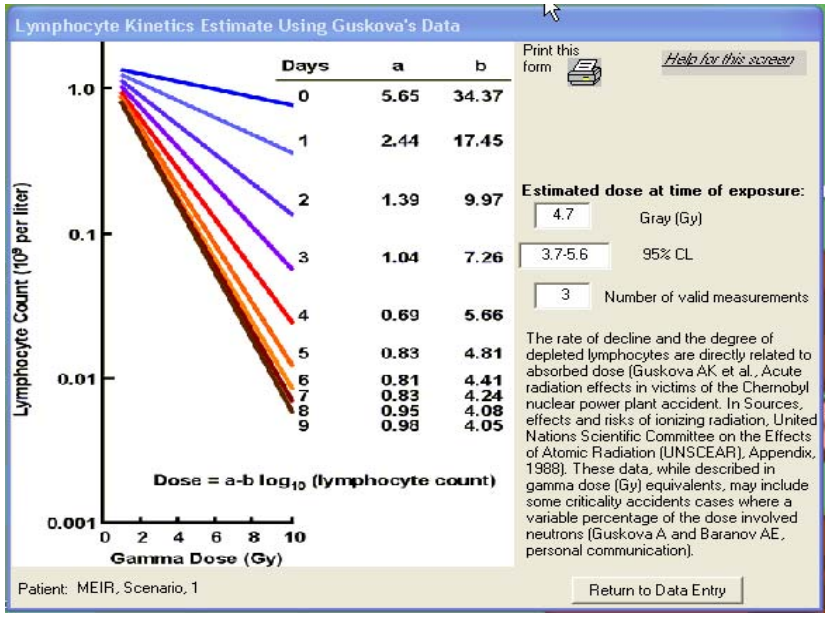
Dose Assessment—Hematologic Indicators

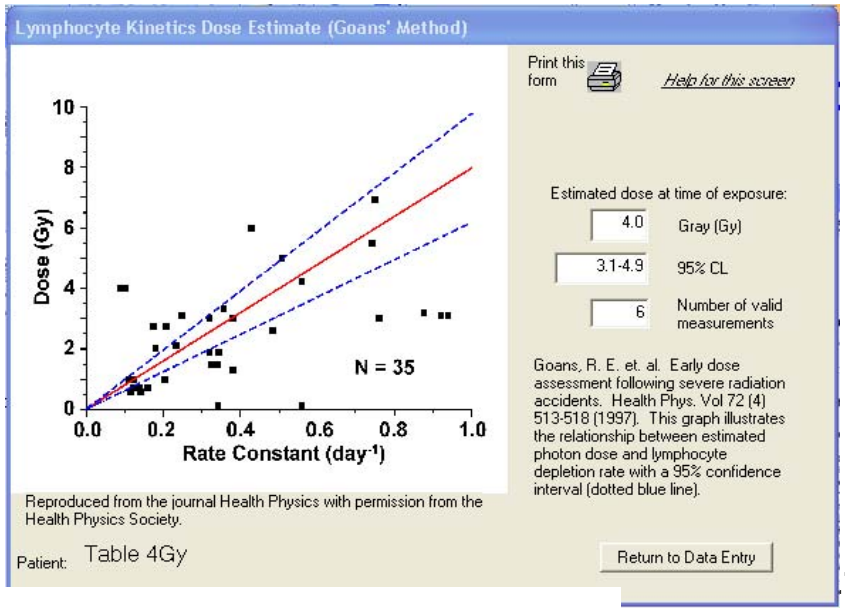


BAT user enters hematology in data entry table and then can convert lymphocyte count to dose estimate.

Dose Predictions Based on Lymphocyte Counts or Lymphocyte Depletion Kinetics







4. Early-response multiple parameter biodosimetry

Table III. Biodosimetry Based on Acute Photon-Equivalent Exposures*

Dose Estimate	Time to Onset of vomiting		Absolute Lymphocyte count ($x10^9$/liter)[b] (Day)						Lymphocyte depletion rate[c]	Relative increase in serum amylase activity at 1 d compared with normals[d]	Number of dicentrics[e]	
Gy	%[a]	Time (Hr)	0.5	1	2	4	6	8	Rate constant		Per 50 metaphases	Per 1000 metaphases
0	--	--	**2.45**	**2.45**	**2.45**	**2.45**	**2.45**	**2.45**	--	1	0.05 – 0.1	1-2
1	19		**2.30**	**2.16**	**1.90**	**1.48**	1.15	0.89	0.126	2	4	88
2	35	4.63	**2.16**	**1.90**	**1.48**	0.89	0.54	0.33	0.252	4	12	234
3	54	2.62	**2.03**	**1.68**	1.15	0.54	0.25	0.12	0.378	6	22	439
4	72	1.74	**1.90**	**1.48**	0.89	0.33	0.12	.044	0.504	10	35	703
5	86	1.27	**1.79**	1.31	0.69	0.20	0.06	.020	00.63	13	51	1034
6	94	0.99	**1.68**	1.15	0.54	0.12	0.03	.006	0.756	15		
7	98	0.79	**1.58**	1.01	0.42	.072	.012	.002	0.881	16.5		
8	99	0.66	**1.48**	0.89	0.33	.044	.006	<.001	1.01	17.5		
9	100	0.56	1.39	0.79	0.25	.030	.003	<.001	1.13	18		
10	100	0.48	1.31	0.70	0.20	.020	.001	<.001	1.26	18.5		

* Table modified from version reported by Waselenko and colleagues [12]. Depicted above are the four most useful elements of biodosimetry. Dose range is based on acute photon-equivalent exposures. The first column indicates the percent of people who vomit, based on dose received and time to onset. The middle left section depicts the time frame for development of lymphopenia. Two or more determinations of blood lymphocyte counts are made to predict a rate constant which is used to estimate exposure dose. The middle right section shows the relative increase in serum amylase activity in humans 1 day after radiation exposure. The final column represents the current "gold standard" which requires several days before results are known. CSF therapy should be initiated when onset of vomiting, lymphocyte depletion kinetics, and/or serum amylase suggests an exposure dose for which treatment is recommended. Therapy may be discontinued if results from chromosome dicentrics analysis indicate lower estimate of whole-body dose.

[a] Cumulative percentage of victims with vomiting.

[b] Normal range: 1.4-3.5x10^9/L. Numbers in bold fall within this range.

Lymphocyte normal range: 1.4-3.5 x 10^9/L

[c] The lymphocyte depletion rate is based on the model Lt = 2.45 x 109/L x e-k(D)t where Lt equals the lymphocyte count ($x10^9$/L), 2.45 x 10^9/L equals a constant representing the consensus mean lymphocyte count in the general population, k equals the lymphocyte depletion rate constant for a specific acute photon dose, and t equals the time after exposure (days).

[d] Relative increases in serum amylase activity compared with normals [42].

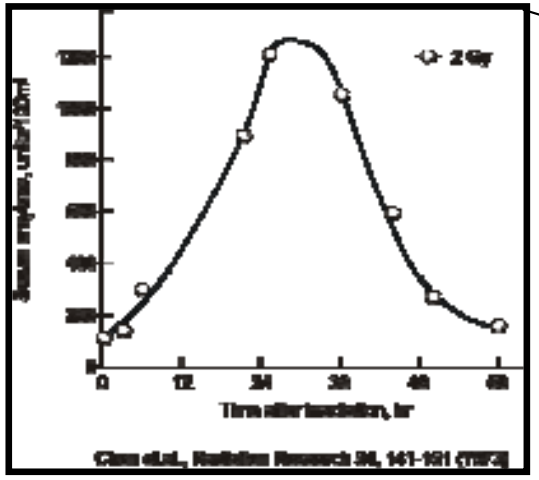
[e] Number of dicentric chromosomes in human peripheral blood lymphocytes.

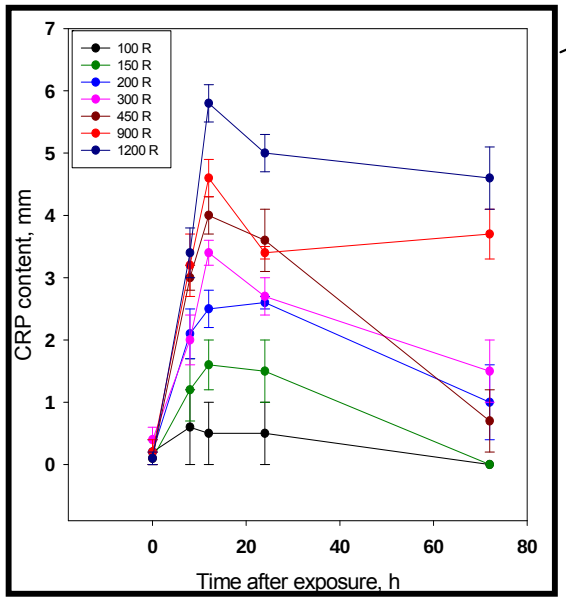
4. Early-response multiple parameter biodosimetry

Radiation Protein Biomarker Concept

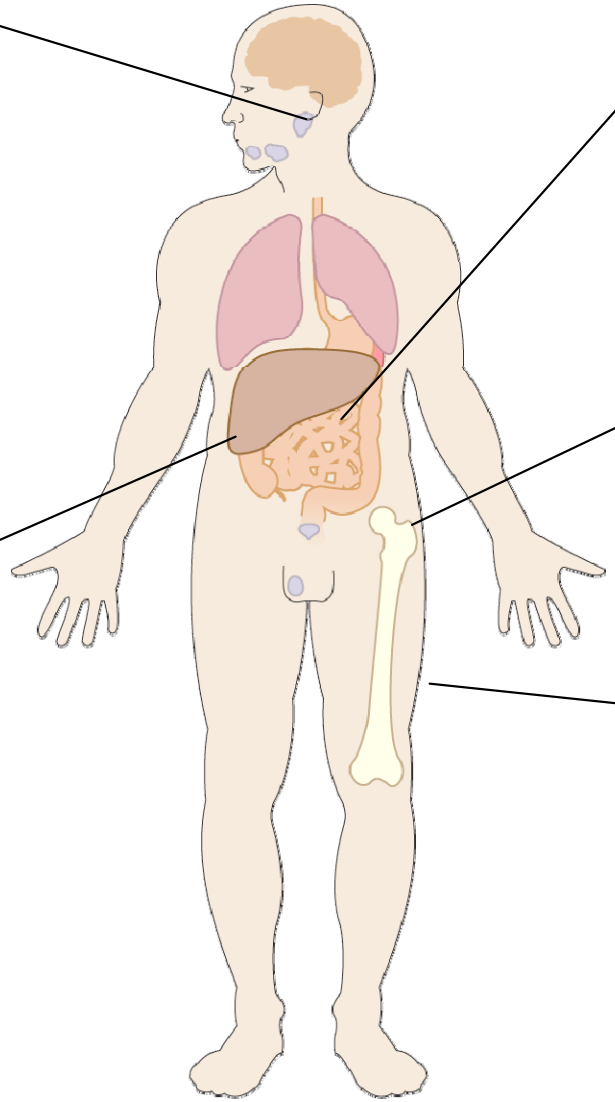
Time Course

Acute Injury Biomarkers

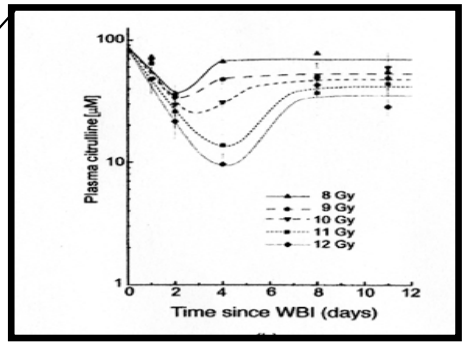




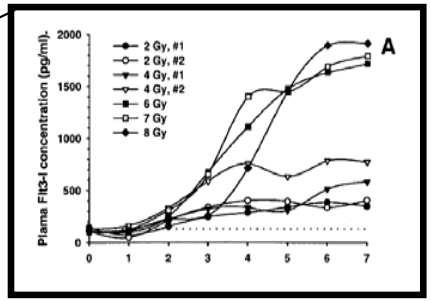
Maltsev *et al*., [Report of Russian Academia of Sciences] 239(3): 750-2, 1978 (in Russian).



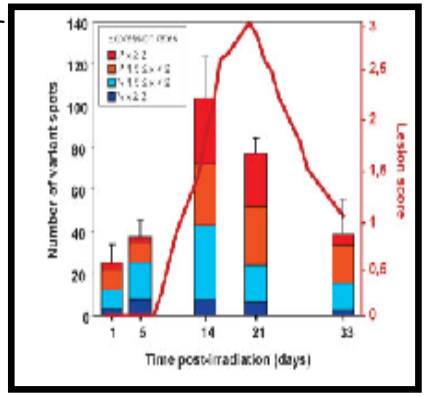
ARS Organ Injury Biomarkers



Lutgens *et al*. IJROBP 57(4): 1067, 2003



Bertho *et al*. IJRB 77(6): 703-712, 2001

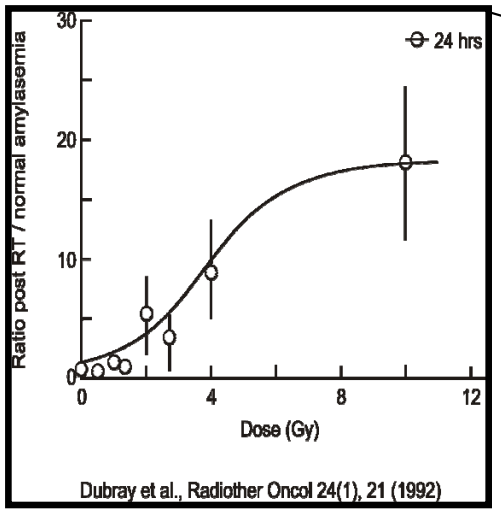


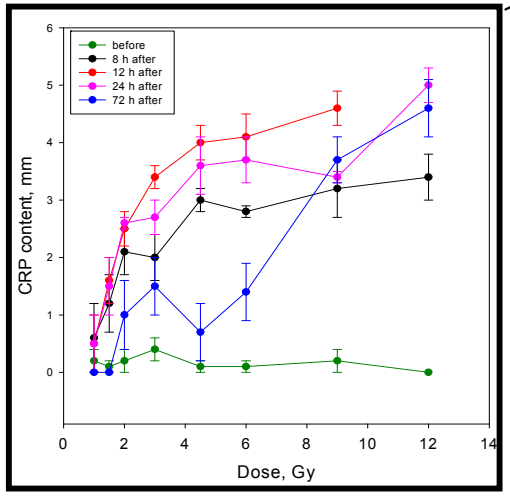
Guipaud et al. Proteomics 7: 3392-4002, 2007

Radiation Protein Biomarker Concept

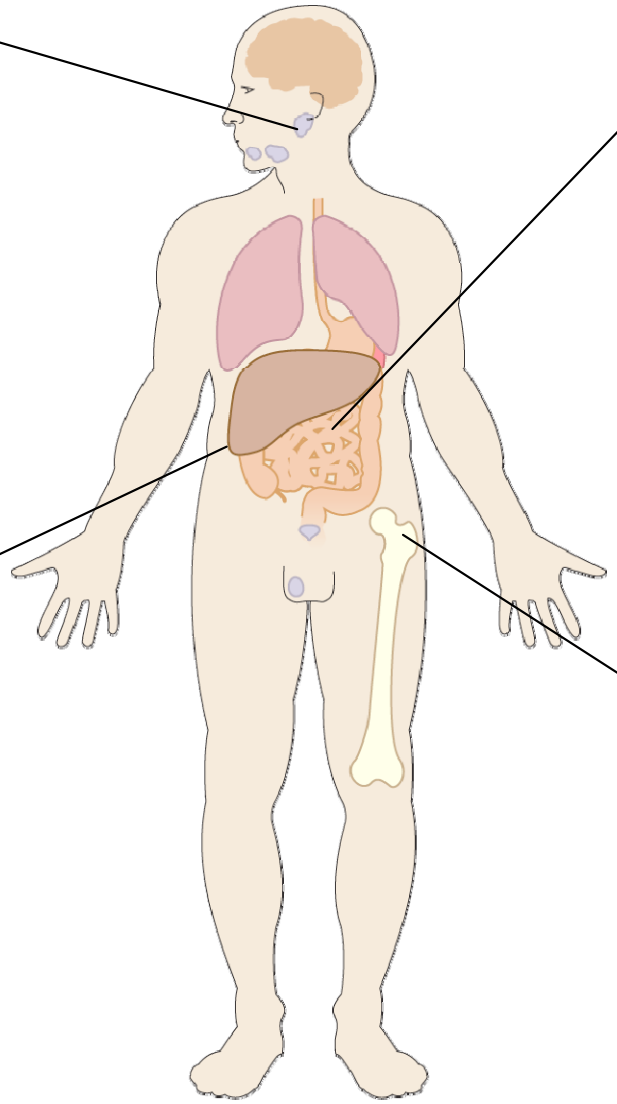
Dose Response

Acute Injury Biomarkers

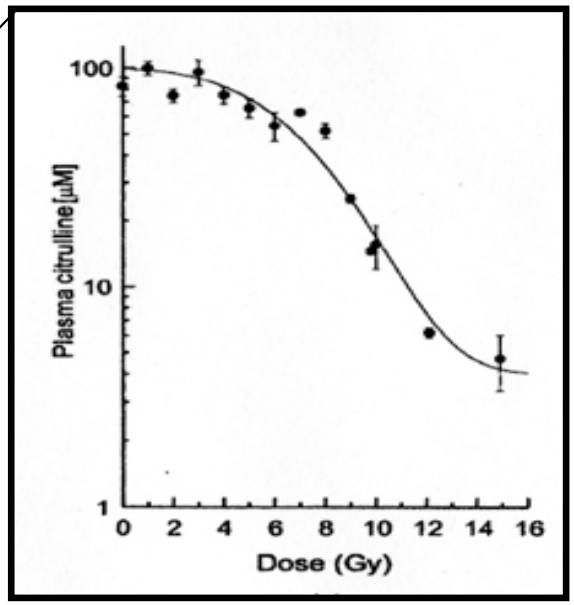




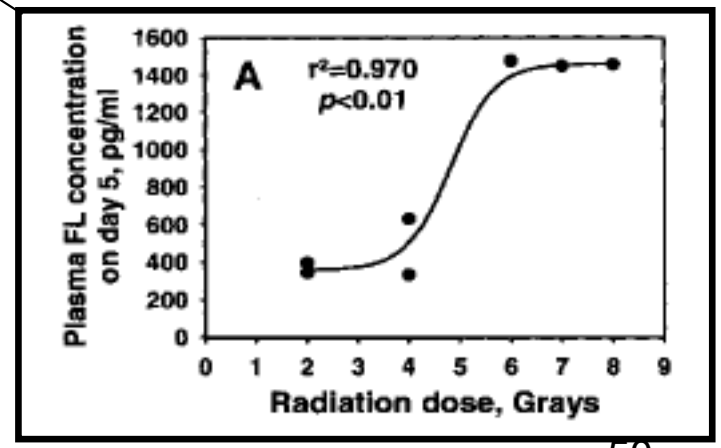
Maltsev et al., [Report of Russian Academia of Sciences] 239(3): 750-2, 1978 (in Russian).



ARS Organ Injury Biomarkers



Lutgens *et al*. IJROBP 57(4): 1067, 2003



Bertho *et al*. IJRB 77(6): 703-712, 2001

First-Responder Radiological Assessment Triage (FRAT)

Outline of Software Application Design

Location-based dose estimate

Dosimeter readings

Dosimetry and radioactivity contamination

Internal contamination

Diagnostic, hospitalization, and mortality messages

Dose assessment

Blood lymphocyte counts

Signs, symptoms and erythema

Vomiting

Diarrhea

Headache

Tachycardia

Consciousness

Body temperature

Weakness

Fatigue

Erythema

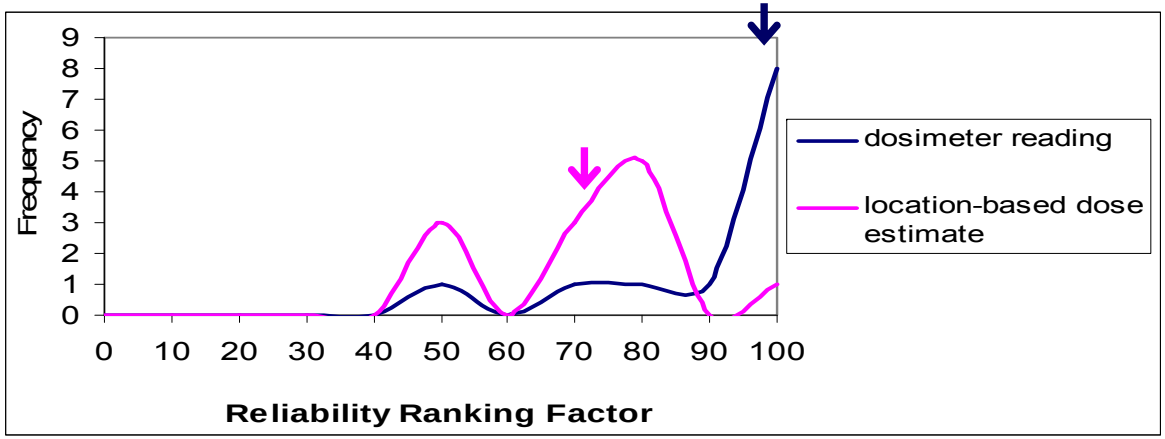
FRAT Expert Panelists

Radiation experts selected by the AFRRI FRAT Team to complete the FRAT survey.

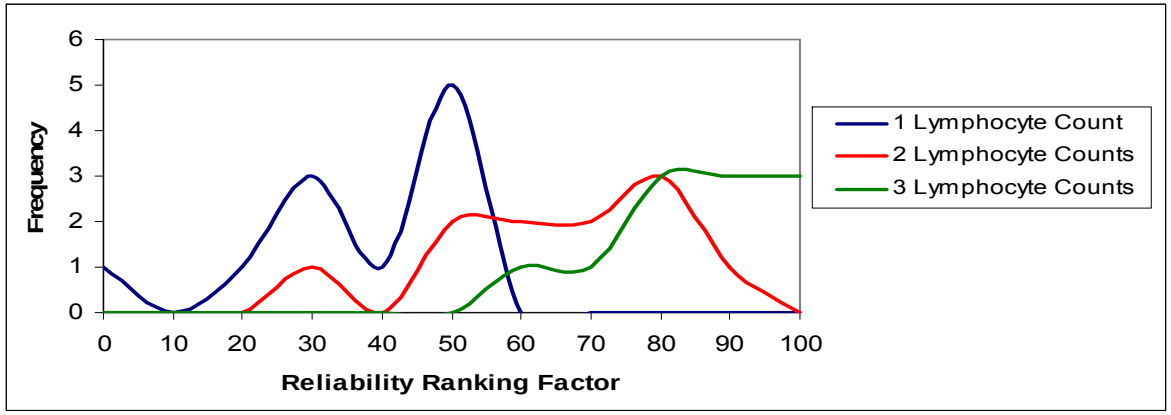
George H. Anno, Ph.D. (Pacific-Sierra Research Corp.)	**William F. Blakely, Ph.D. (AFRRI)**	**Elena Buglova, M.D. (IAEA)**
Nicholas Dainiak, M.D. (Bridgeport Hospital)	**William E. Dickerson, M.D. (AFRRI)**	**David Holt, Ph.D. (Institute of Naval Medicine, United Kingdom)**
John Jacocks, M.D. (Army Test and Evaluation Command)	**Pataje G.S. Prasanna, Ph.D. (AFRRI)**	**Charles A. Salter, Ph.D. (AFRRI)**
Vijay K. Singh, Ph.D. (AFRRI)	**Horace Tsu, M.D. (AFRRI)**	**Govert P. van der Schans (The Netherlands Organization for Applied Scientific Research - Prins Maurits Laboratory)**

Frequency Distribution Diagrams of FRAT Expert Panelist Consensus Survey Results

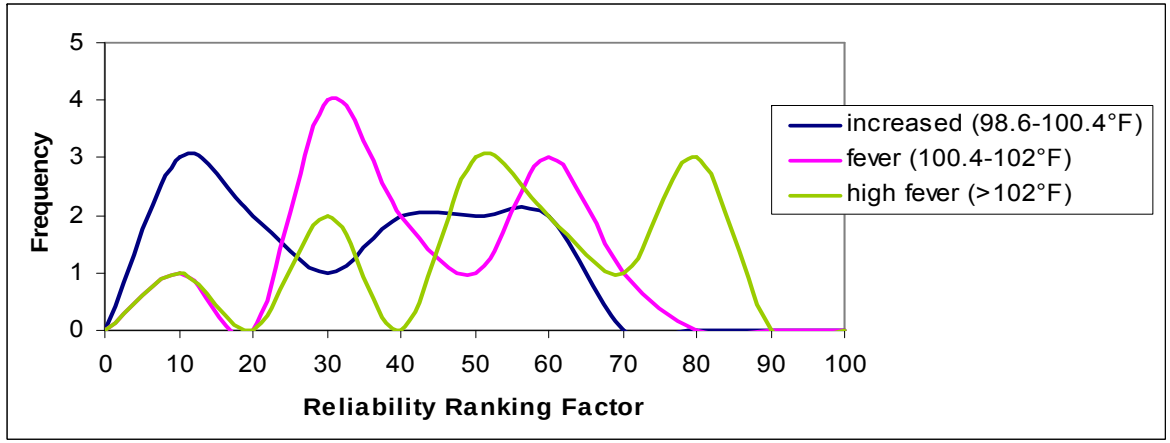
Dosimetry



Lymphocyte Counts

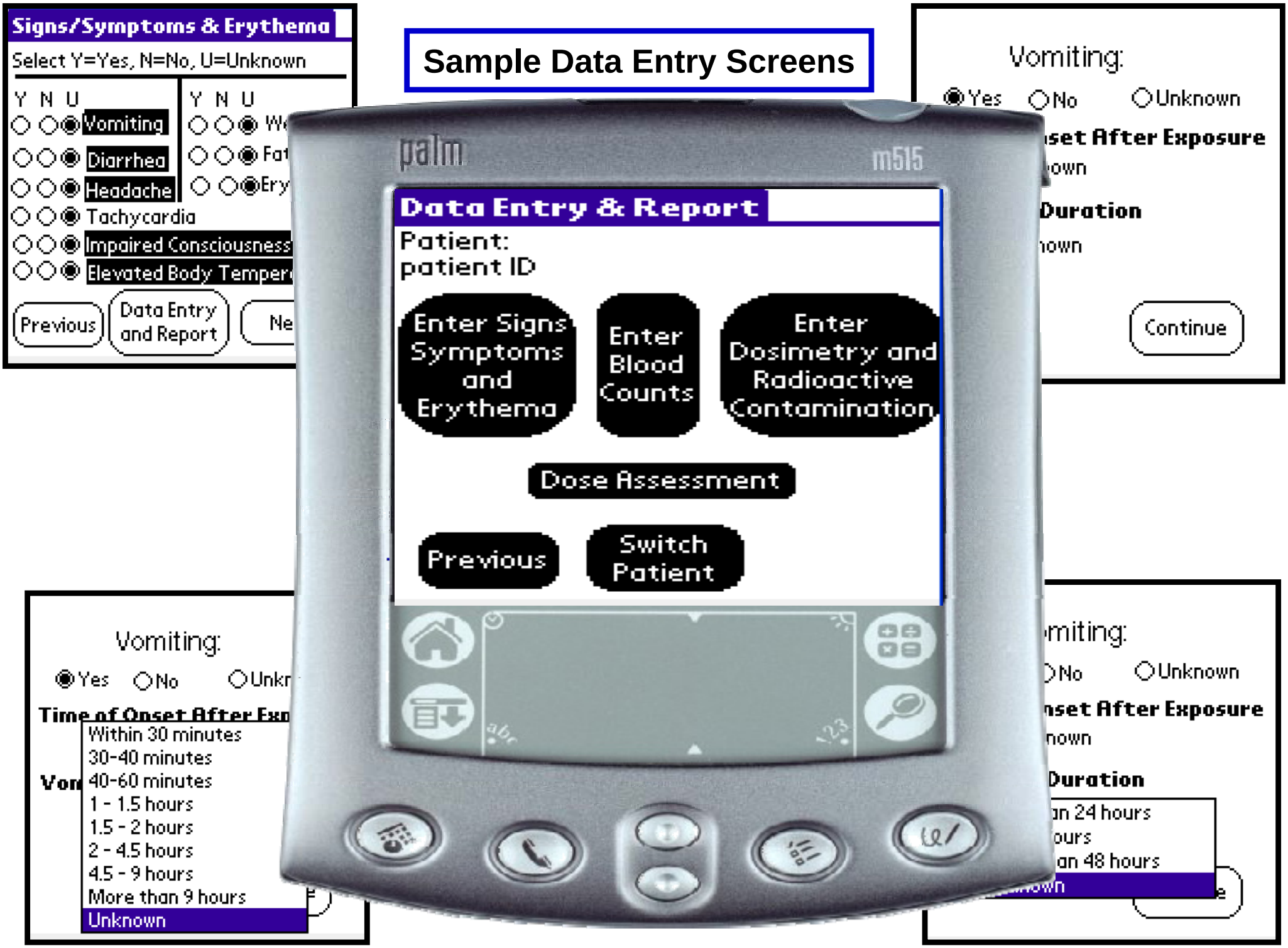


Body Temperature



Arrows show median response (sample size, n = 12).

Sample Data Entry Screens



FRAT Triage Dose Assessment Pages

Triage Dose Assessment – 1

Patient: MEIR, Scenario, 1

Radiation OVEREXPOSURE -- potentially SEVERE medical effect.

All results are based on acute whole body photon exposures of healthy subjects without medical treatment.

POOR Reliability

Next

Triage Dose Assessment – 2

Patient: MEIR, Scenario, 1

Lymphocyte Message:

Draw serial blood samples and make additional lymphocyte measurements. Determination of

Previous

POOR Reliability

Next

Triage Dose Assessment – 3

Patient: MEIR, Scenario, 1

CATEGORY	Est. Dose (cGy)
Signs and Symptoms	160.0
Dosimetry	
Blood Lymphocyte Counts	465.7
Pooled	**408.4**
95% Confidence	239.7 - 577.1

Previous

POOR Reliability

Next

Triage Dose Assessment – 4

Patient: MEIR, Scenario, 1

Reliability/Diagnostic Message:

The multiparameter triage exposure or dose estimate has POOR reliability based on the FRAT triage parameters. Additional patient signs and symptoms,blood cell counts, and

Previous

POOR Reliability

Next

Triage Dose Assessment – 5

Patient: MEIR, Scenario, 1

Hospitalization & Mortality Msg

Hospitalization (90%) for 60-90 days with 0-80% fatality risk in 3-12 weeks without extensive treatment.

Previous

POOR Reliability

Next

First-responder's Radiological Assessment Tool - (FRAT)

- **Handheld software for estimation of potential radiation exposure**
- **Small, <200 kb**
- **Uses Palm OS**
- **FRAT and other products available at AFRRI website http://www.afrri.usuhs.mil.**

Summary of Entered Data — Screen 14

File Window Help

SUMMARY

Dose estimates and measurements are shown in Red

Patient: MEIR, Scenario, 1
Military unit or organization: United States Army
Filename: MEIR Scenario 1.mdb

Help on this screen

Prodromal (Gy)

☑ Symptoms — Onset of vomiting (h): 7.00

Estimated dose: 1.5 — ☐ Antiemesis therapy prior to initial vomiting

95% CL: 1.1-1.9

About prodromal estimates

Radioactive Contamination

☐ Internal Sampling
☐ External Sampling
☐ Chelation/Blocking Therapy

Infection

☐ Infection
☐ Therapy

Eryth/Wound

☐ Erythema
☐ Wound

Hematology (Photon Equivalent Gy)

	Hours	Dose (Gy)	N	95% CL
Multiple:		4.7	3	3.7-5.6
Individual 1st:				
Individual 2nd:				

☐ Cytokine therapy

About hematology estimates

Lymphocyte Cytogenetics

	#	Dose (Gy)	95% CL
▶	1		
	2		
	3		

Physical Dosimetry (Sv)

	#	Shallow Dose Equiv	Deep Dose Eq Photon	Deep Dose Eq Neutron	Comm Eff Dose Equiv	Total Eff Dose Equiv
▶	1					
	2					
	3					

Expert's Assigned Individual Dose

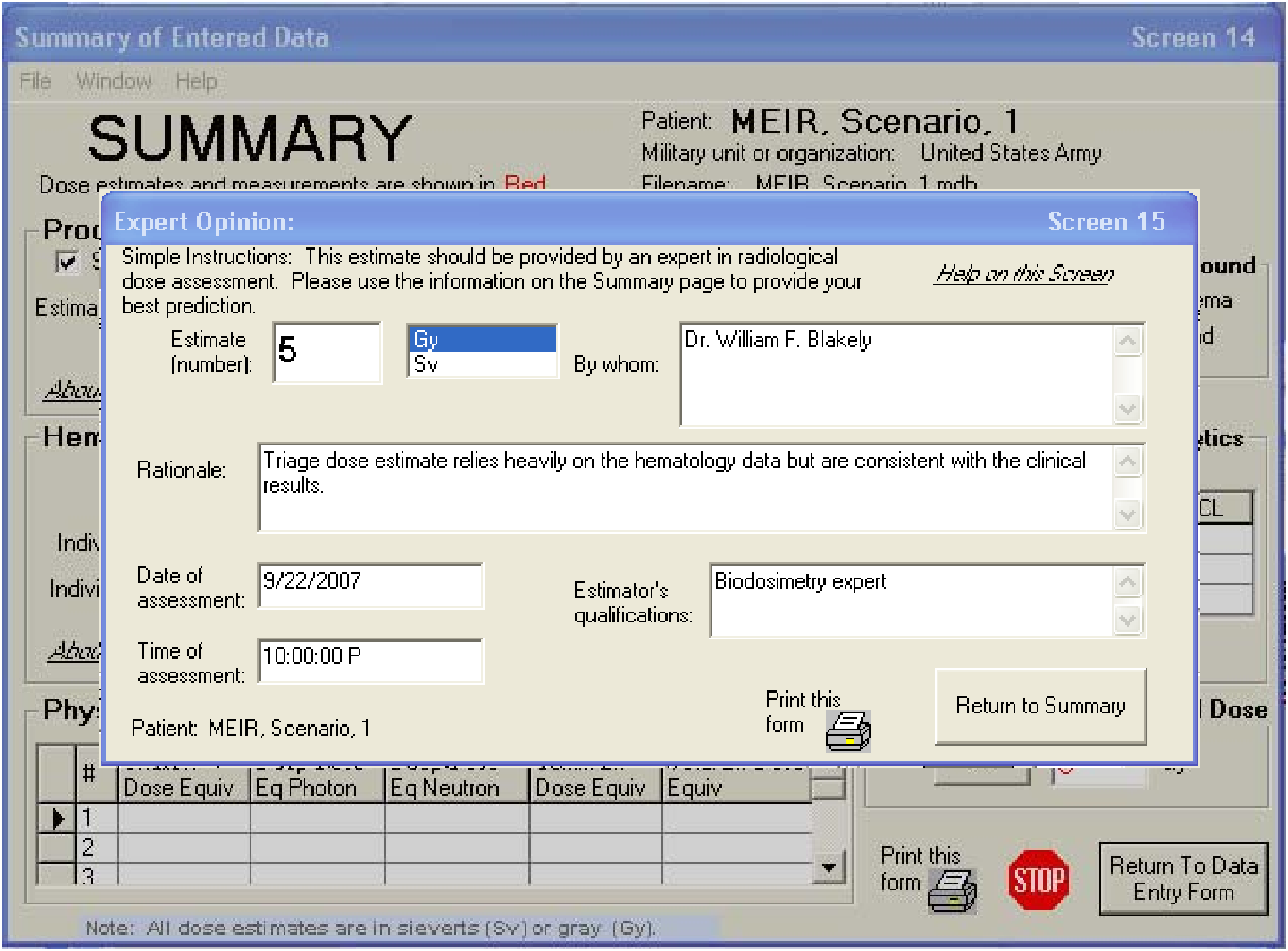
Set — 5 Gy

Print this form

STOP

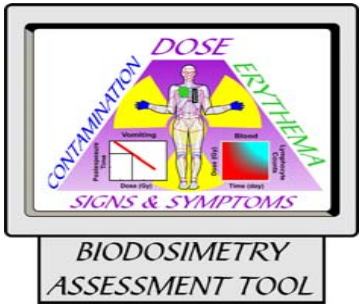
Return To Data Entry Form

Note: All dose estimates are in sieverts (Sv) or gray (Gy).


Summary of Entered Data
Screen 14
File Window Help
SUMMARY
Patient: MEIR, Scenario, 1
Military unit or organization: United States Army
Filename: MEIR_Scenario_1.mdb
Dose estimates and measurements are shown in Red
Expert Opinion:
Screen 15
Simple Instructions: This estimate should be provided by an expert in radiological dose assessment. Please use the information on the Summary page to provide your best prediction.
Help on this Screen
Estimate (number):
5
Gy
Sv
By whom:
Dr. William F. Blakely
Rationale:
Triage dose estimate relies heavily on the hematology data but are consistent with the clinical results.
Date of assessment:
9/22/2007
Estimator's qualifications:
Biodosimetry expert
Time of assessment:
10:00:00 P
Patient: MEIR, Scenario, 1
Print this form
Return to Summary
Dose Equiv Eq Photon Eq Neutron Dose Equiv Equiv
1
2
3
Print this form
STOP
Return To Data Entry Form
Note: All dose estimates are in sieverts (Sv) or gray (Gy).

Biodosimetry Assessment Tool

Windows OS



Website Download

CDROM Release

Technical Support Working Group

Distributed by TSWG's Developer's of First Responder Software Applications

Palm PDA

Palm OS

First-responders Radiological Assessment Triage (FRAT)

The First-responders Radiological Assessment Triage (FRAT) software application for the Palm OS is being designed specifically for use by first responders and will provide general guidance and triage dose assessment tools. The information will be based on the components of the radiation pocket guide and will require minimal text entry.

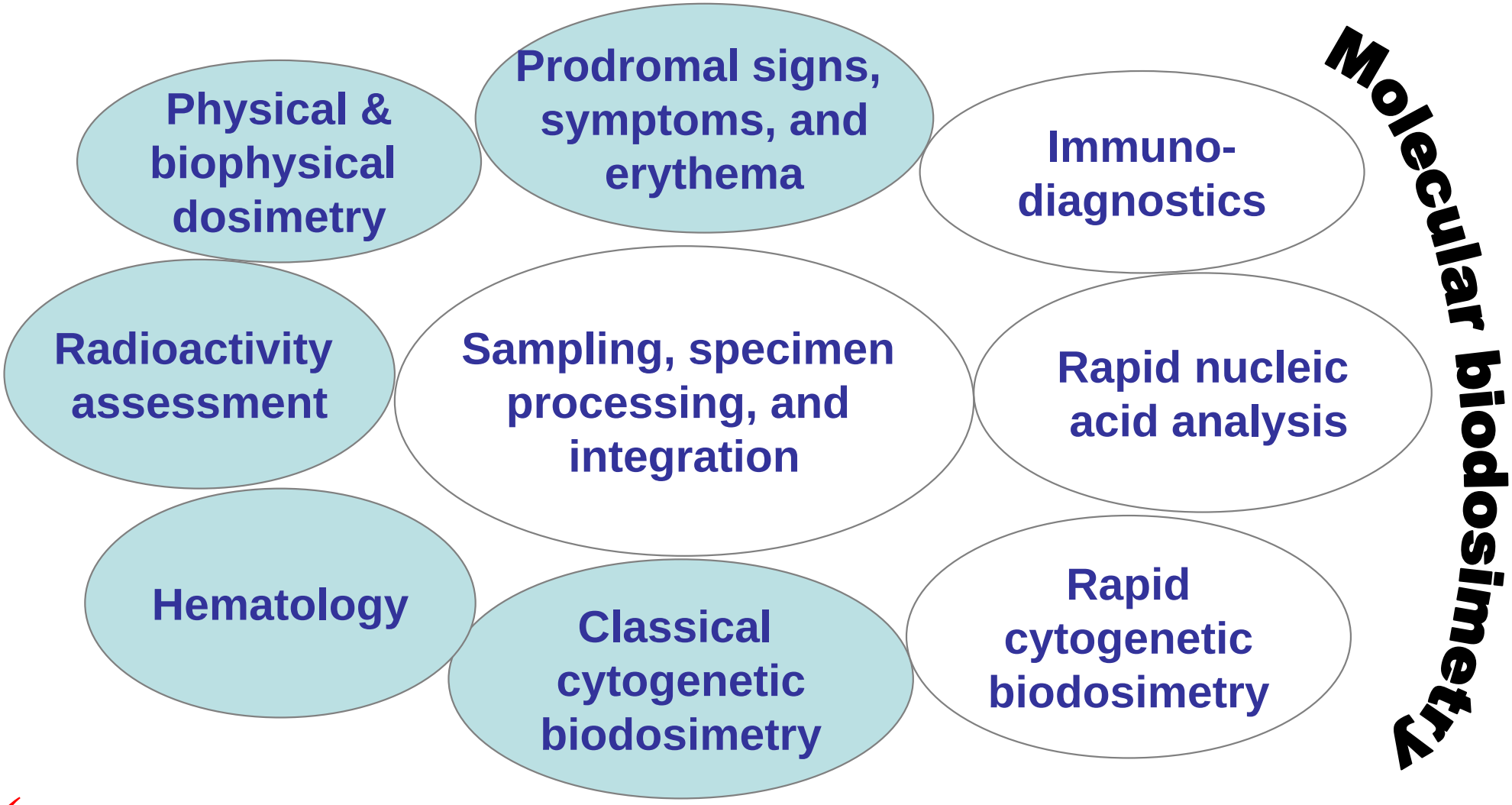
4. Early-response multiple parameter biodosimetry

Provisional and Emerging Triage, Clinical, and Definitive Dose Assessment Methods

Table IV. Select List of Provisional and Emerging Radiation Injury and Dose Assessment Methods		
Method	Status	References
EPR		
- teeth (*in vivo*)	EPR L-band is potentially able to measure doses as low as 2 to 3 Gy but needs additional development	2; 54-56
- nails (*ex vivo*)	EPR X-band shows a lower limit of detection of 0.5 - 1 Gy	2; 57-59
Blood protein immunoassay		
- C-reactive protein	Acute-phase reaction protein derived from liver and demonstrated both as a biodosimeter and bioindicator of hematology ARS	60-62
- Flt-3 ligand	Bioindicator of bone marrow injury	63-64
- Citrulline	Bioindicator of injury to small intestine epithelial tissue	65-67
- γH2AX	Protein associated with DNA double strand break repair	68
- Multiple proteins	Candidate multiple protein biomarkers proposed for biodosimetry; multiple protein biomarkers demonstrated using multivariate discriminant or linear regression analyses methodology for radiation injury	69-70
Blood lymphocytes gene expression		
- QRT-PCR assay of multiple targets	Multiple radiation responsive gene targets identified and used in the development of consensus dose-response calibration curves using an *ex vivo* blood radiation model system	71-75

4. Early-response multiple parameter biodosimetry

Integrated Biodosimetry and Diagnostic Systems



✓ **No single assay is sufficient to address potential radiation exposure scenarios that are complex and involve mass casualties.**

✓ **Triage, clinical, and definitive radiation biodosimetry all require multiple bioassays and analytic technologies designed for use in both chemical, biological, radiological, and environmental (CBRE) diagnostics and general medical care.**

4. Early-response multiple parameter biodosimetry

Recommended Enhancements

- Local, national, and international cooperation to: a) train and equip first responders/receivers in radiological triage, b) establish deployable teams, and c) access specialize reference laboratories.
- Participation in radiological exercises and UN agencies outreach programs (RANET, REMPAN) including global networks of reference laboratories (i.e., BioDoseNet).
- Identification and validation of biomarkers for biodosimetry and biophysical dosimetry methods to permit rapid radiological triage, leading towards licensed and effective hand-held and laboratory devices for assessing radiation exposure.
- Incorporation of “biodosimetry operations” into the first responders “all hazard” response concept.

Summary

- **A coordinated integration of local and national radiological response capabilities that are supplemented with international cooperation can provide critical biological dosimetry capabilities to support the medical management of a mass-casualty radiological emergency.**
- **Major gaps in the biodosimetry response capability for mass-casualty radiological emergencies have been identified and include:**

  - the capability to rapidly identify exposed individuals using licensed diagnostic hand-held or field-laboratory systems;

  - protocols to measure radioisotopes likely used by terrorists from contaminated individuals;

  - enhance assess to deployable radiological teams with capabilities to perform on-site haematology, assessment of clinical signs and symptoms, and sampling for radiobioassays;

  - funding to establish and sustain functional global networks of expert reference laboratories performing dose assessment.
- **International cooperation will enhance biological dosimetry capabilities through sharing of research discoveries, nations participating in U.N. agencies radiological assistance programs, and research efforts focusing on applications for applied radiological biodosimetry.**