The National Academies of Sciences and National Cancer Institute, 2014 Gilbert W. Beebe Symposium, The Science and Response to a Nuclear Reactor Accident, Keck Center of the National Academies, Washington , D.C., 13 May 2014

Emergency Biodosimetry

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UNIFORMED SERVICES UNIVERSITY
of the Health Sciences
Armed Forces Radiobiology Research Institute

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

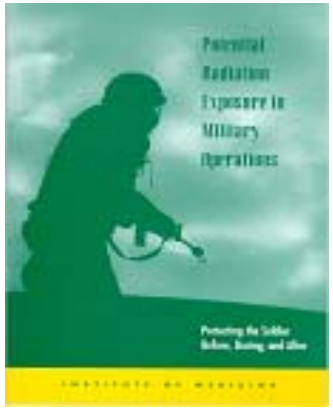
Commercial Manufacturer	Financial Interest	Comments
BioRad, Careside, etc.	None	Equipment evaluation
Various companies developing 1st responder software applications	None	Interactions with Technical Support Working Group developers
Meso Scale Diagnostics	None	Co-Investigator on BARDA contract to develop radiation responsive biomarker device for radiation dose assessment

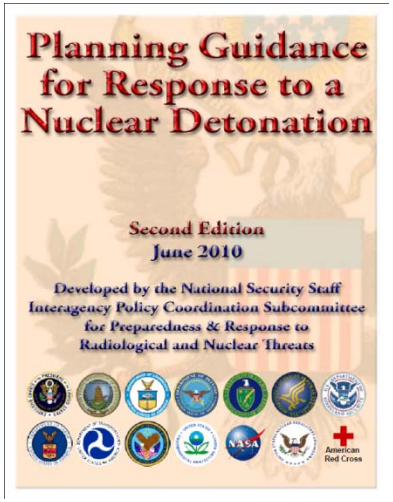
The opinions, conclusions, and recommendations expressed or implied do not necessarily reflect the views of the Department of Defense or any other department or agency of the federal government.

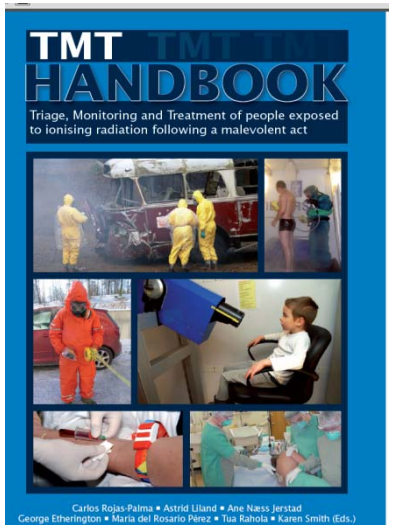
Taskings

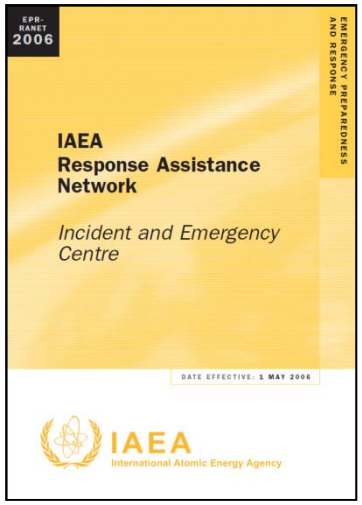
- What are the current recommended applications of biodosimetry in a nuclear power plant accident for workers, accident responders, and general public that are suspected of exposure to radiation?
- Describe the concept of operations for biodosimetry.
- What are the current limitations and gaps in biodosimetry?

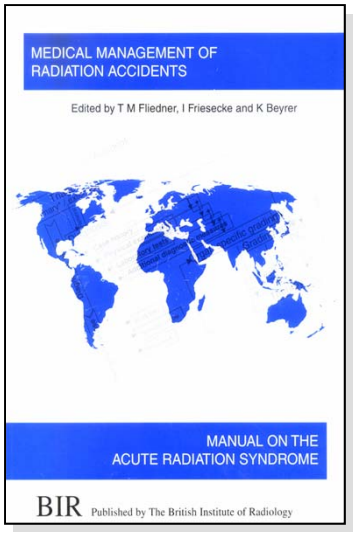
Guidance and Doctrine – I
Multiple Parameter Biodosimetry

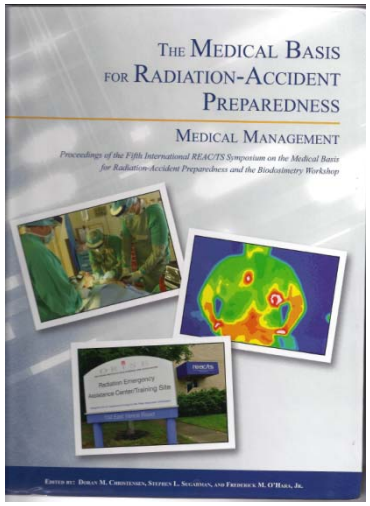


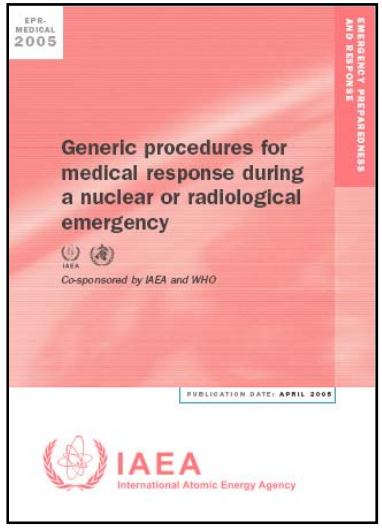


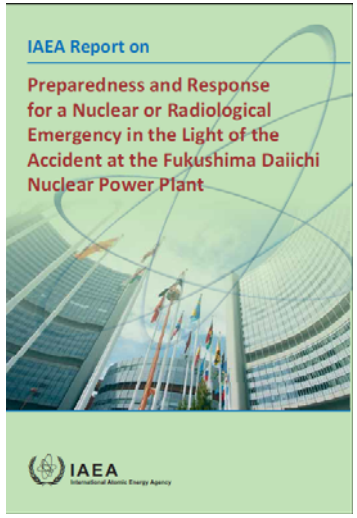




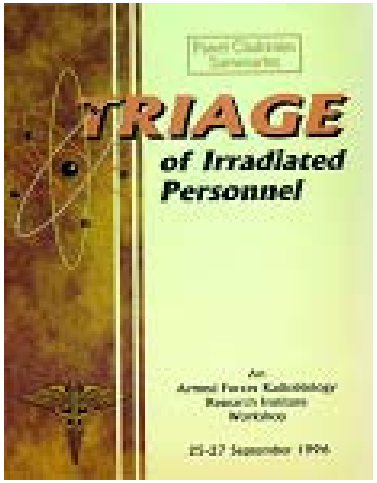


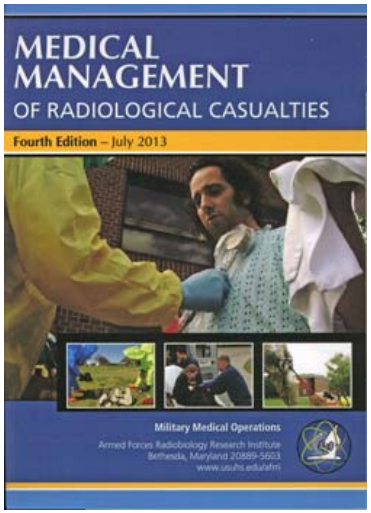






Guidance and Doctrine – II
Multiple Parameter Biodosimetry

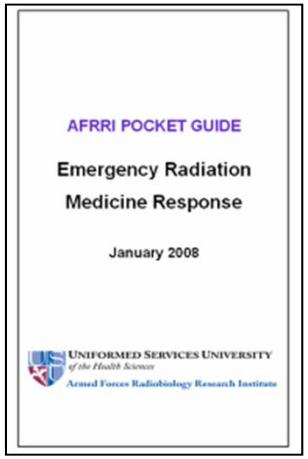


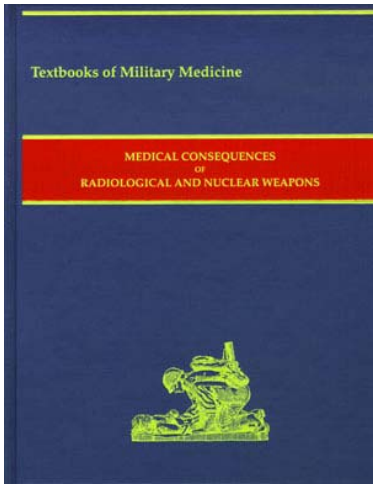


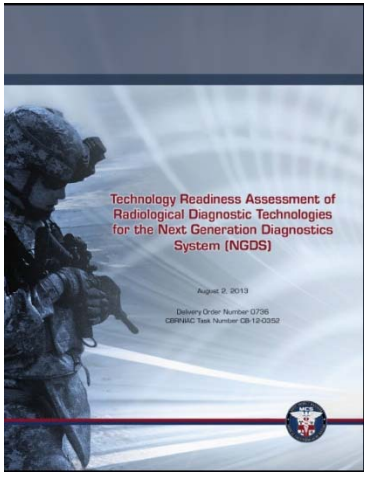
DoD

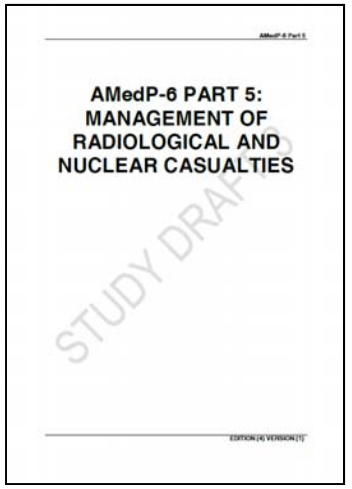
NUCLEAR WEAPON ACCIDENT RESPONSE PROCEDURES (NARP) MANUAL

August 22, 2013

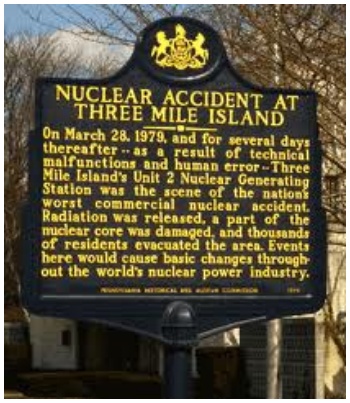








Nuclear Reactor Accidents



Biodosimetry for potential radiation overexposures involving:

- Nuclear Power Plant Workers
- Accident Responders
- Local Population

Bouville A, **Linet MS**, Hatch M, Mabuchi K, and **Simon SL**. Guidelines for exposure assessment in health risk studies following a nuclear reactor accident. Environ Health Perspectives 122(1): 1-5, 2014

Biodosimetry – General Guidance

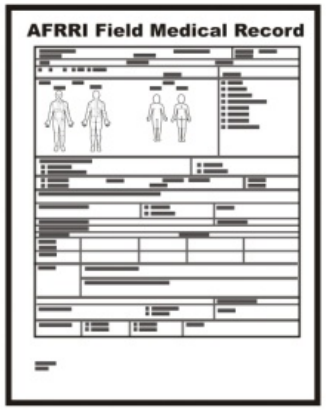
- Perform measurements, if appropriate, to determine radionuclide contamination and record physical dosimetry measurements, if available
- Observe and record prodromal signs (erythema) and symptoms
- Obtain CBC with white blood cell differential immediately, then every 6 hours for 2-3 days, and then 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

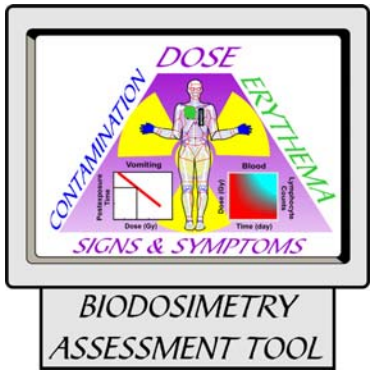
Blakely WF, Salter CA, Prasanna PG. Health Physics 89(5):494–504, 2005.
Waselenko JK, MacVittie TJ, Blakely WF, et al. *Ann Intern Med*. 140(12):1037–1051, 2004.

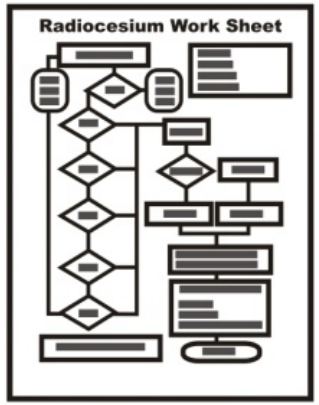
Acute-phase Patient Assessment Methods

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., CRP, amylase activity)	< 3 min		<$2	**Yes (CRP)**	3-7	1-4
- 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	**Yes**	3-7	1-4
Area Monitoring						
- dosimetry results (e.g. TLDs, aerial measurements) combined with personal location information	**Unknown**	-			**3-7**	

Medical Recording Worksheets and Software Tools







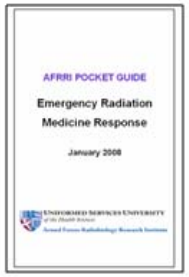
WinFRAT

REMM

AFRRI website: www.usuhs.edu/afrri/

REMM website: www.remm.nlm.gov/index.html

Biodosimetry Concept of Operations

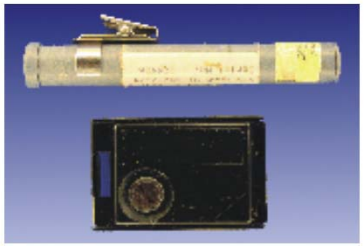


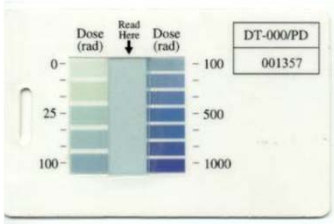
Blakely et al. Health Physics 99 (suppl 3): S184-S191, 2010

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

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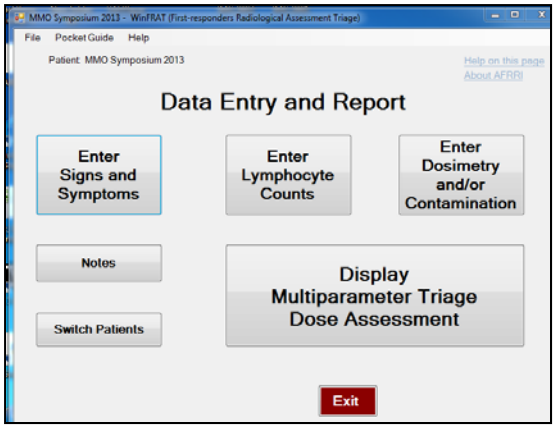
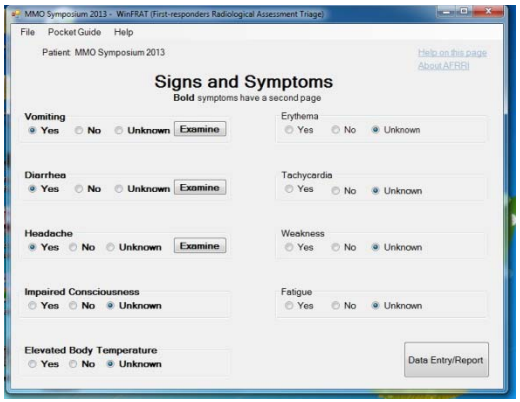
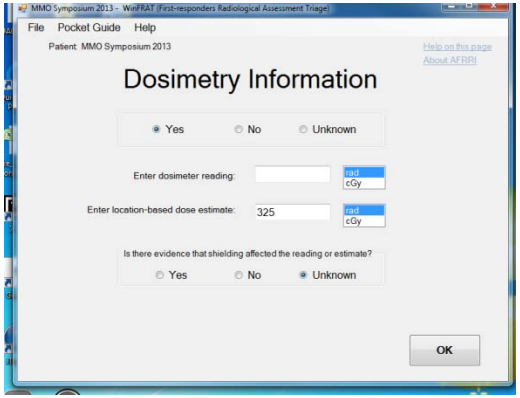
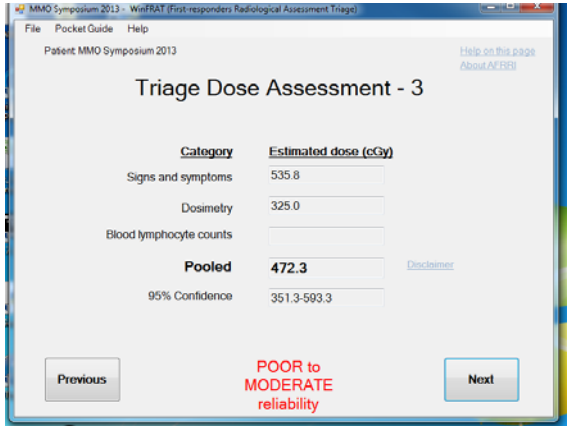
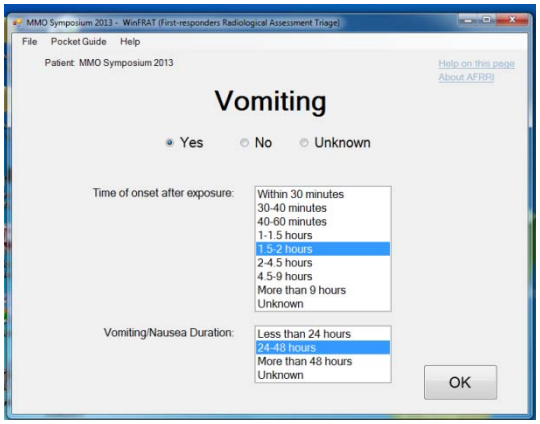
First-responders Radiological Assessment Triage

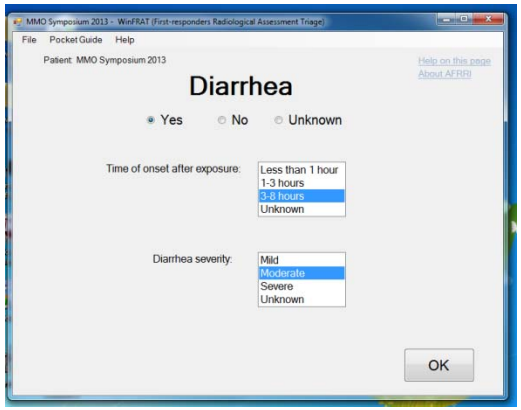


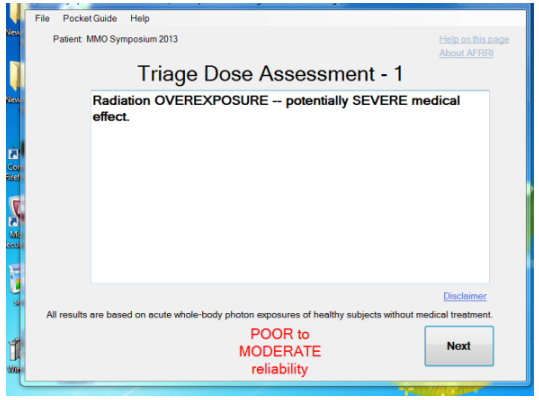












HemoCue® WBC Systems

www.hemocue.com/us/Products/White_Blood_Cell_count-220.html

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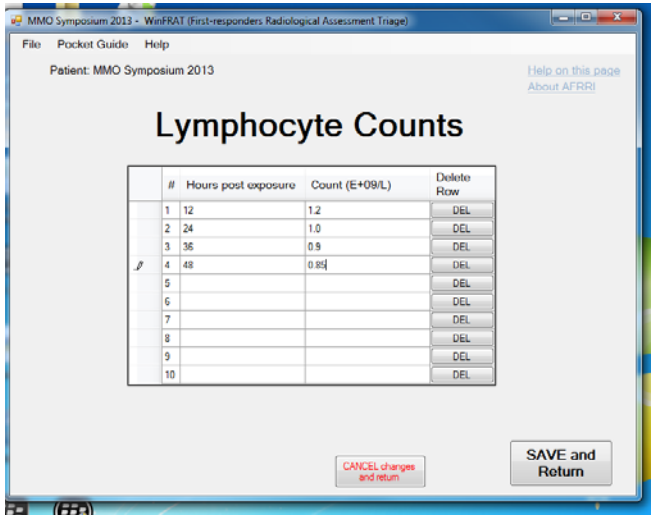
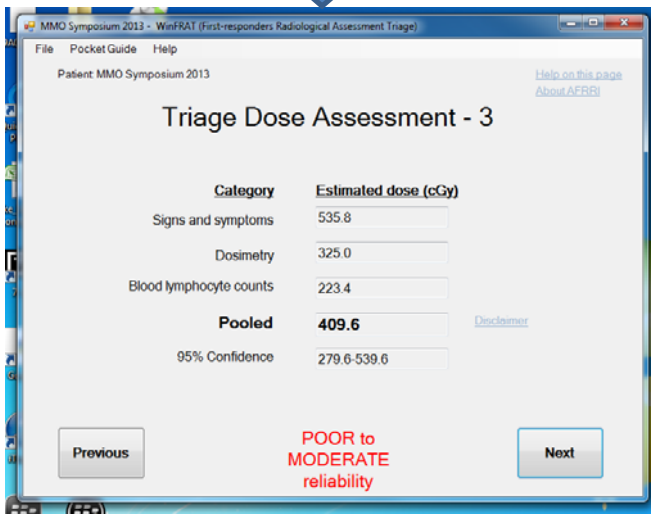
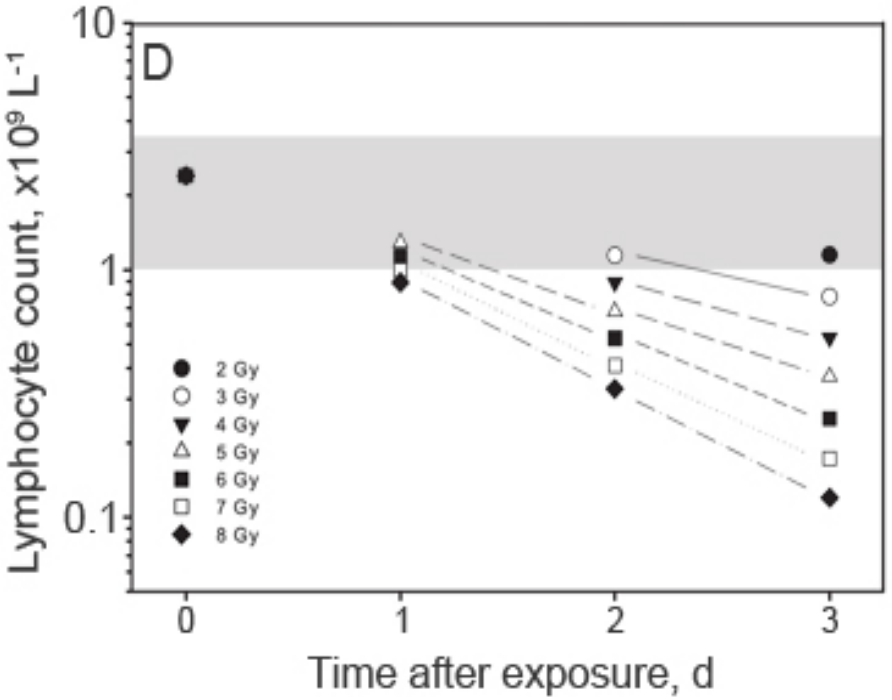
First-responders Radiological Assessment Triage



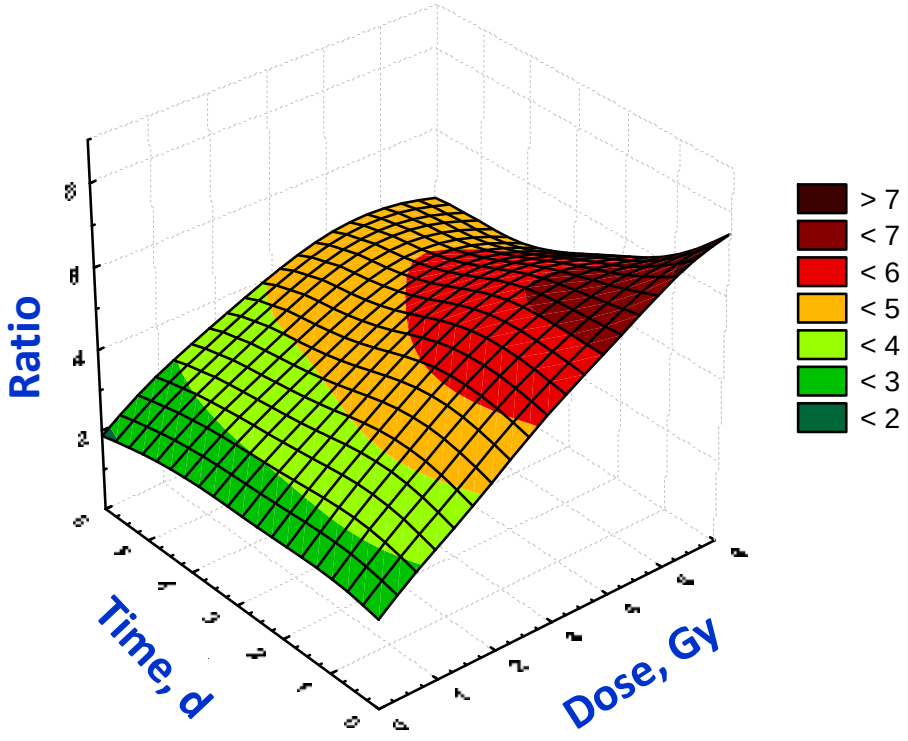


Biodosimetry Based on Hematology

Lymphocyte Counts



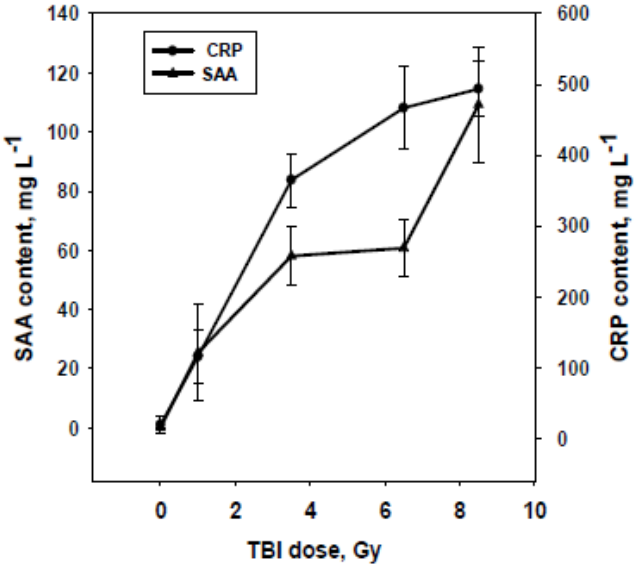
Neutrophil to Lymphocyte Ratio

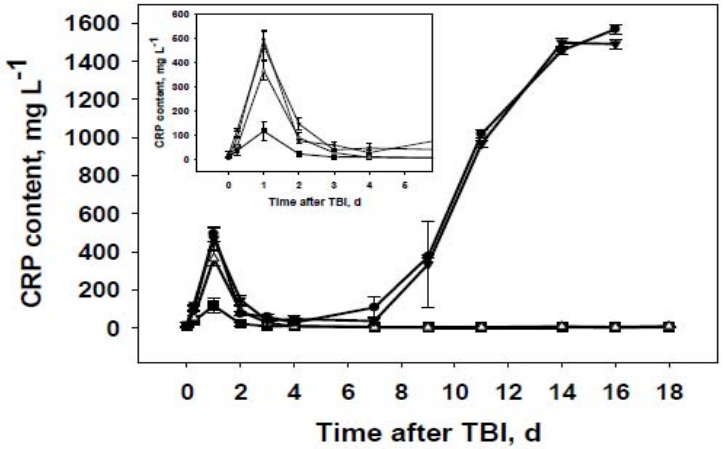


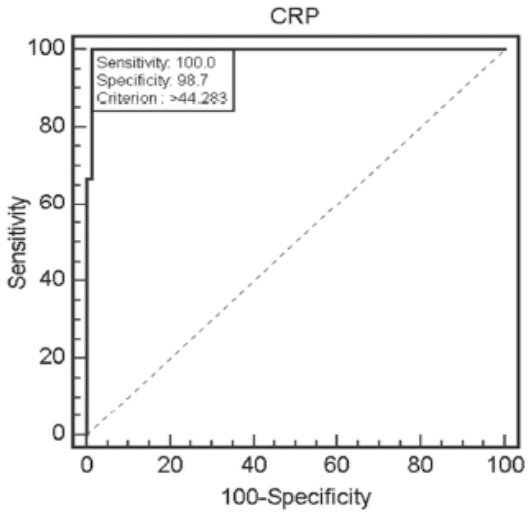
Title: C - reactive protein and Serum Amyloid A as Early-phase and Prognostic Indicators of Acute Radiation Exposure in Nonhuman Primate Total-body Irradiation Model

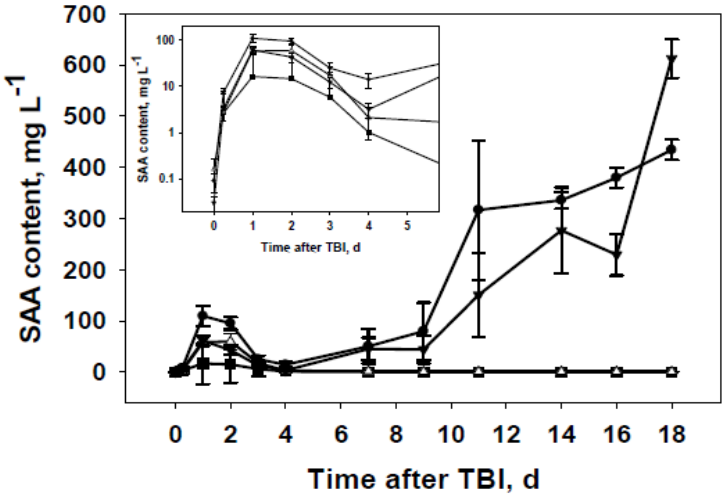
Authors: N.I. Ossetrova, D.J. Sandgren, W.F. Blakely

Radiation Measurements (2011), doi:10.1016/j.radmeas.2011.05.021









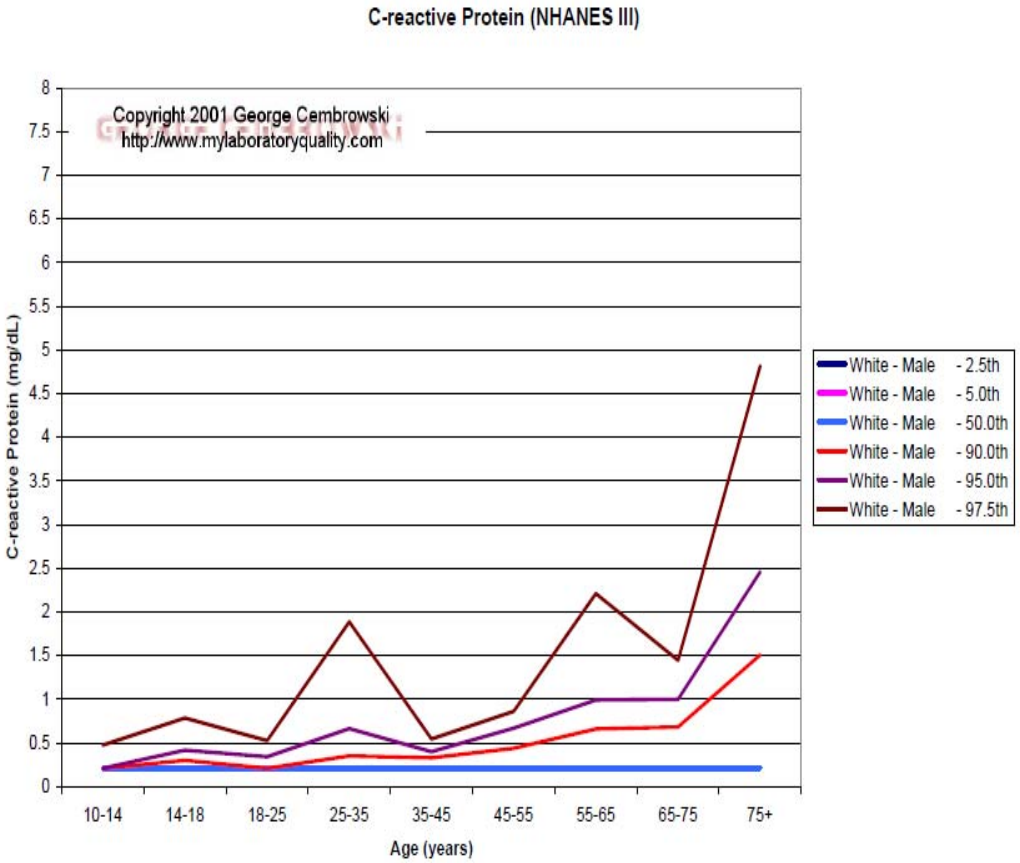
Radiological Triage Concept Using CRP
(Ossetrova and Blakely)

Rapid FDA Approved Devices

Orion
CRP Quick Kit

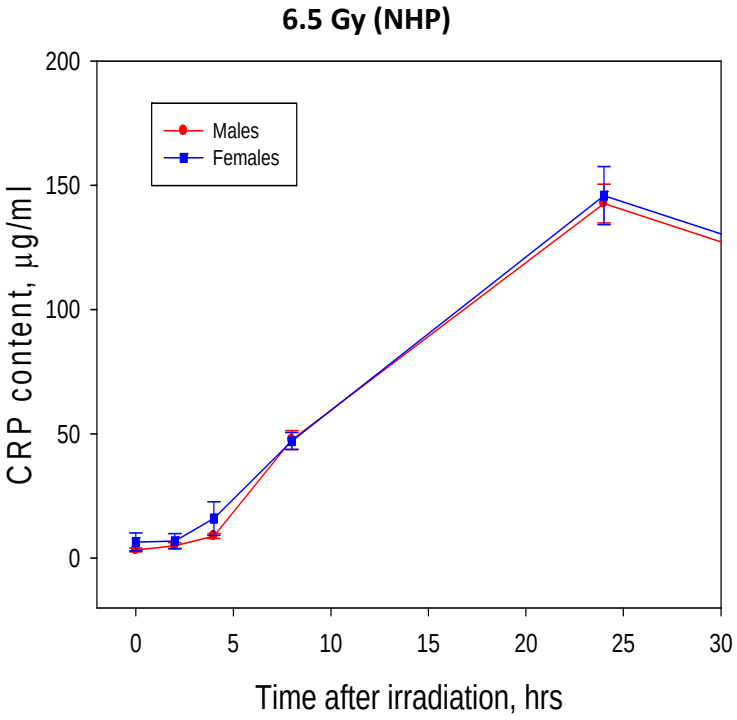
Stanbio Laboratory
CRP test kit

Low human baseline levels



Radiological Triage Concept Using CRP
(Ossetrova and Blakely)

High signal to noise



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

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).

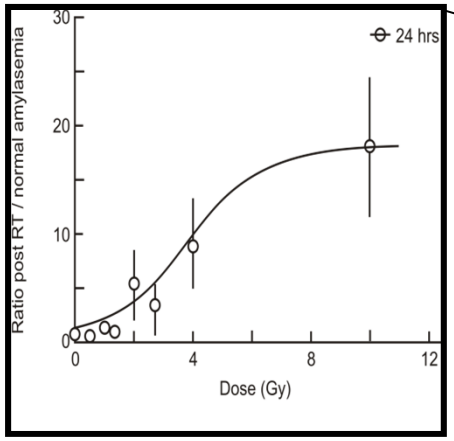
Degree of ARS	CRP level ≥ 1 mm	CRP level: 0.5 mm	CRP level 0 mm	Total (row)
3-4	26	9	17	52
2	6	7	19	32
0-1	3	18	23	44
Total (column)	35	34	59	128

Mal'tsev VN *et al*. [The individual prognosis of the gravity and of the outcome of radiation disease on immunological indexes], Radiation Biology. Radioecology, 46(2), 152-158, 2006 (in Russian).

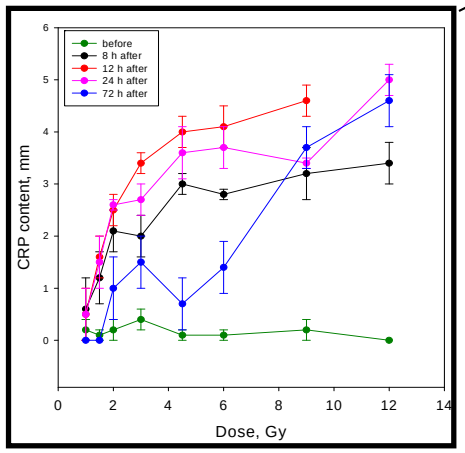
Radiation Protein Biomarker Concept

Dose Response

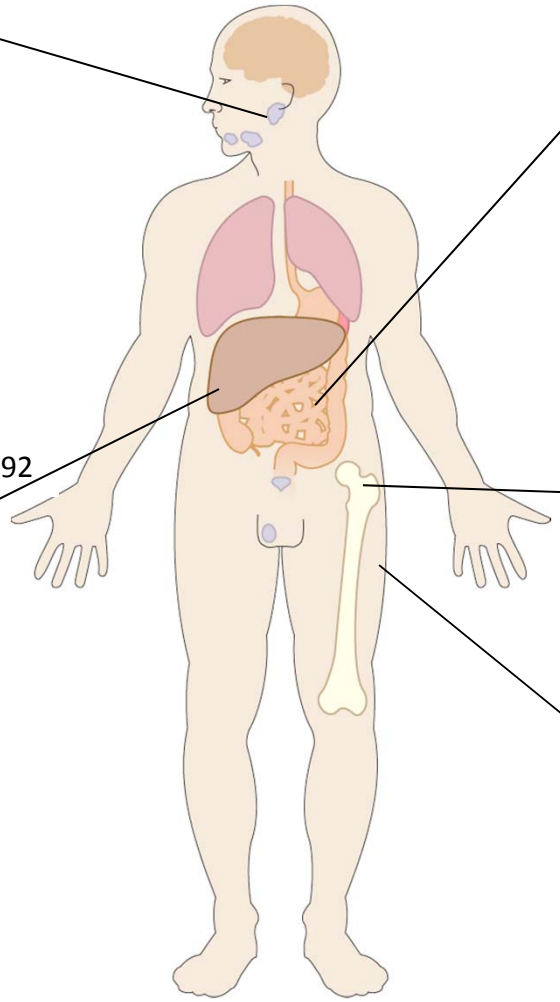
Acute Injury Biomarkers



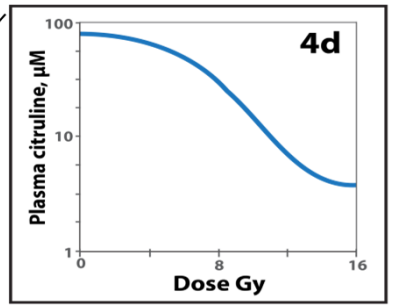
Dubray *et al*., Radiother. Oncol. 24(1):21-6, 1992



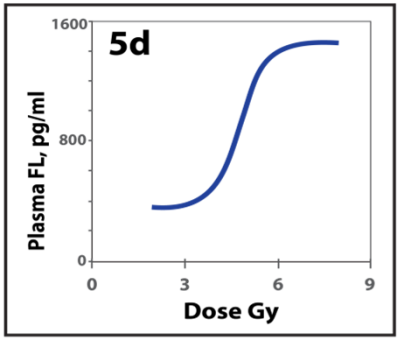
Maltsev *et al*., [Report of Russian Academia of Sciences] 239(3): 750-2, 1978 (in Russian).



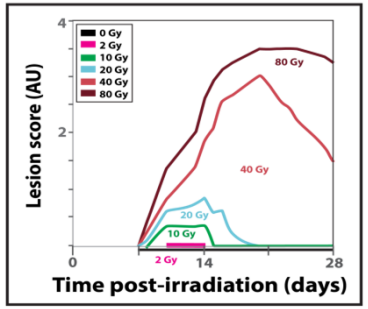
ARS Organ Injury Biomarkers



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

METREPOL PLUS

(Sequential Diagnostic)

Biomarkers (organ specific)

Neurovascular System:
Oxysteril 24S-hydrocholesterol

Haematopoietic System:
Flt-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

Gastroinestinal System:
Serum or urinary amylase activity
Citrulline
Neurotension
Gastrin hormones
CRP
SAA
Osysterrol 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)

$N_i\ H_i\ C_i\ G_i$

Response Category

$RC=?_{xd}$

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.

Example:

N2 → N2 H3 C1 G2 → $RC=3_{2d}$

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

Degree of severity to describe the extent of damage

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

Modified from T. M. Fliedner et al. (Edit.): Medical Management of Radiation Accidents: Manual on the Acute Radiation Syndrome. British Institute of Radiology, London, 2001

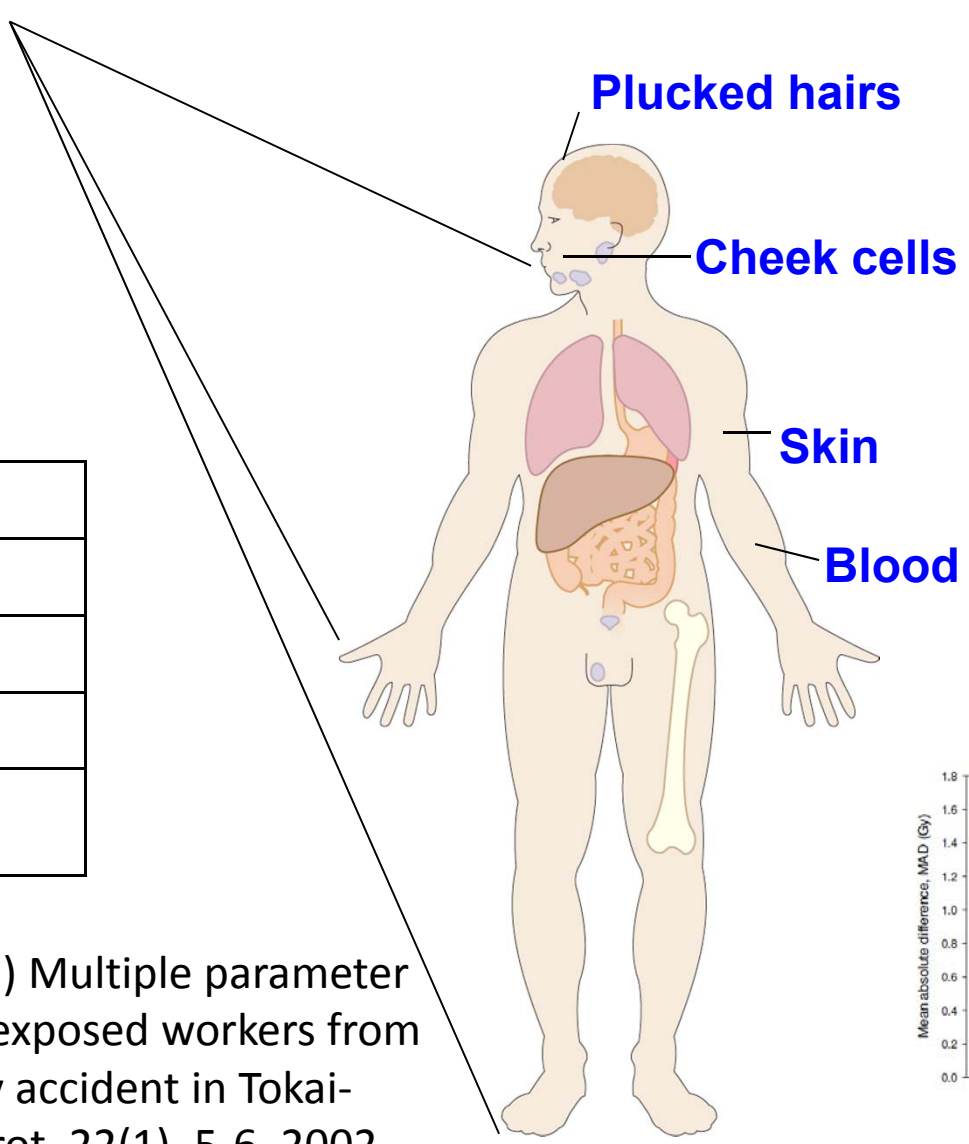
Multiple Parameter Radiation Biodosimetry

EPR Dosimetry

In vivo
Ex vivo

Bioassays to determine radionuclide contamination

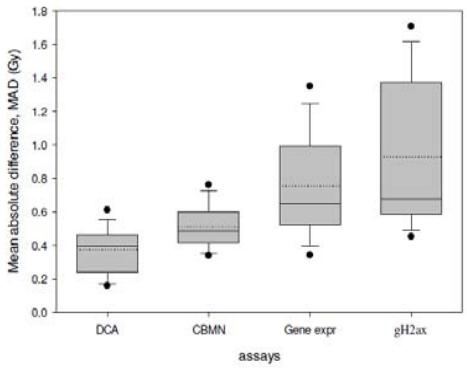
Urine
Fecal
Blood
Nasal
Oral



Cytogenetic Assays

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

NATO Exercise



Blakely WF (2002) Multiple parameter biodosimetry of exposed workers from the JCO criticality accident in Tokai-mura, J. Radio. Prot. 22(1), 5-6, 2002.

Rothkamm et al. Rad Res 180: 111-119, 2013

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

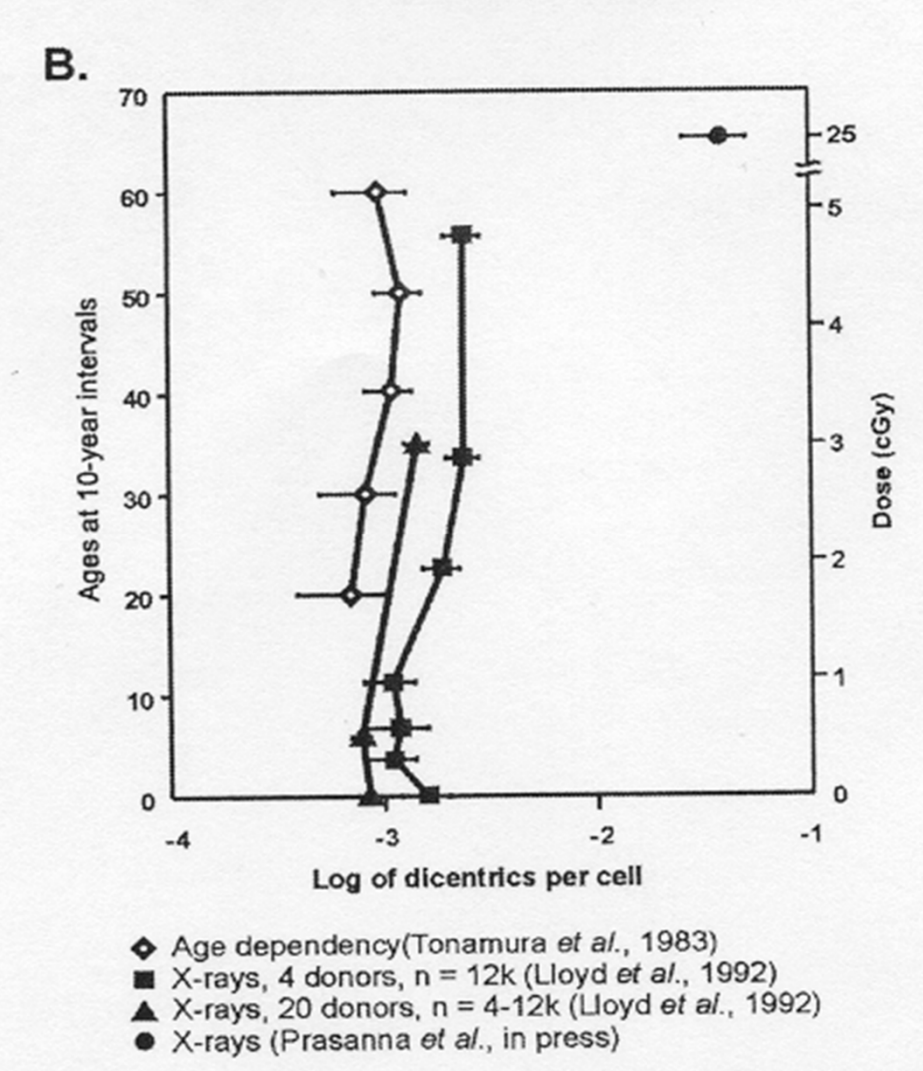
  - Livingston and colleagues (REAC/TS)

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

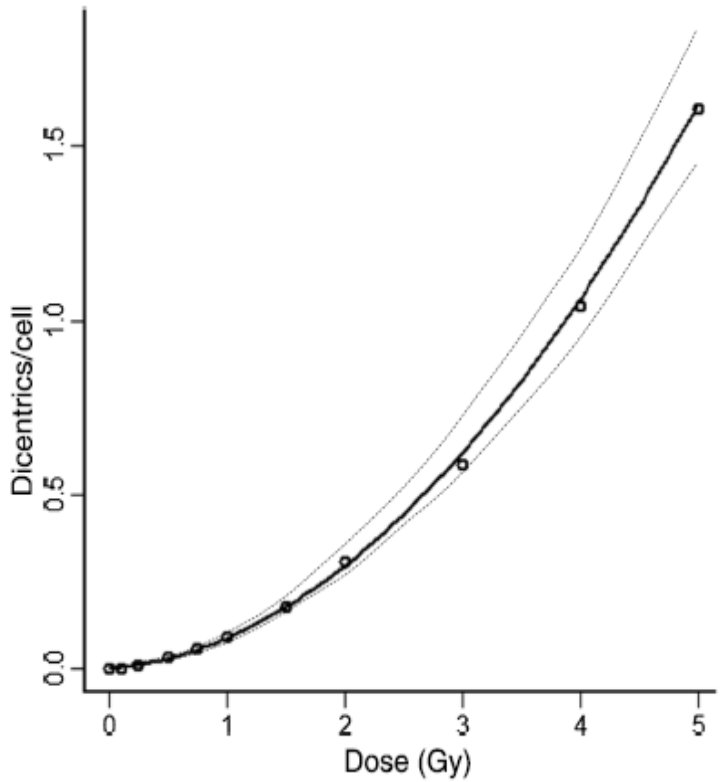
  - UK/France/Germany; Japan; Canada; USA; Latin America; South Korea

Lymphocyte - Dicentric Assay

Effect of Age and Low-Radiation Doses



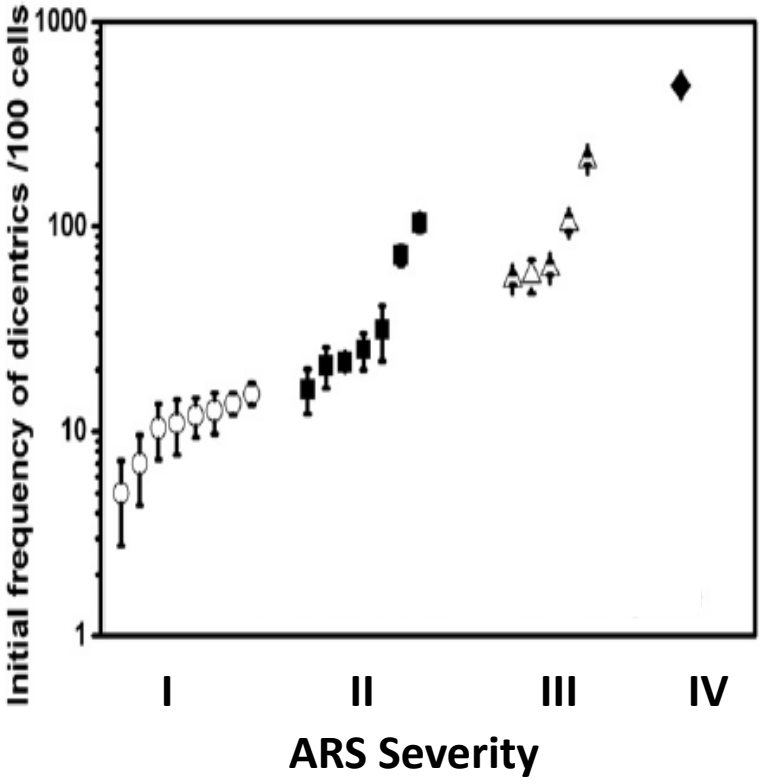
Dose Response Calibration Curve



Suto et al. Health Phys 105(4): 366, 2013

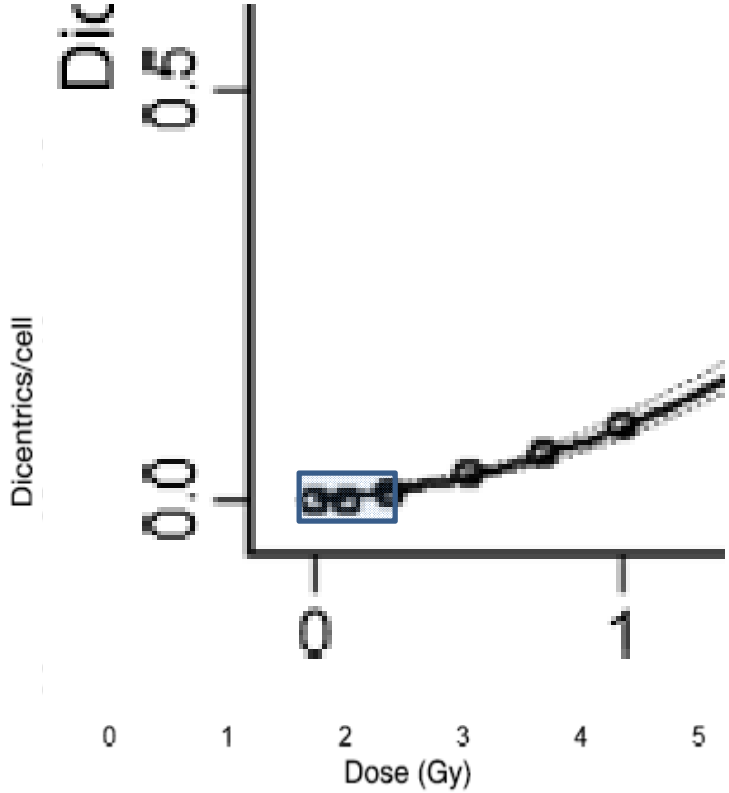
Lymphocyte - Dicentric Assay

Early Dicentric Yields: Grade of ARS Severity (Chernobyl)



Khvostunov LK, Sevan'kaev AV, Llyod DC, Nugis VY, and Voisin P (2011) Radiat Meas 46(9): 832-826.

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



Suto et al. Health Phys 105(4): 366, 2013

FDA Approved Biodosimetry Device For Early Medical Management Treatment Decisions

- **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**

Benjamin Franklin

“If you fail to plan,
you are planning to fail!”