

# Chapter 6

## EARLY-PHASE BIOLOGICAL DOSIMETRY

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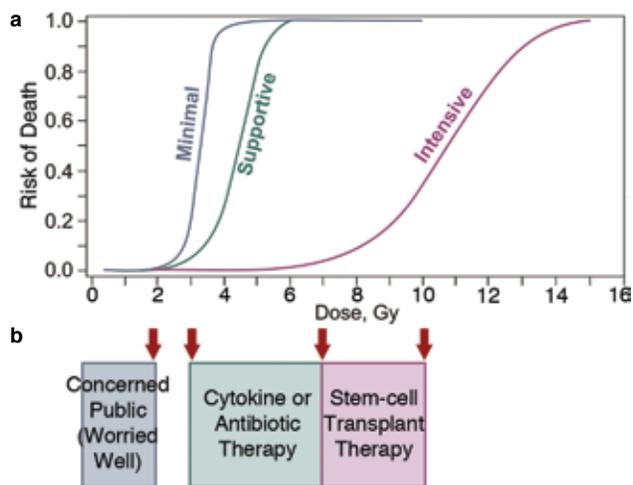
## INTRODUCTION

Biological dosimetry is radiation dose or injury assessment using clinical signs and symptoms, including bioindicators from the hematological, gastrointestinal (GI), cerebrovascular, and cutaneous systems; radiation biomarkers (ie, chromosome aberrations measured in mitogen-stimulated peripheral blood lymphocytes), and other available biodosimetry approaches.<sup>1</sup> Alternative biodosimetry assessment methods can include measuring absorbed dose in solid matrix materials (ie, teeth enamel, bone, nail clippings) from suspected exposed individuals. For example, absorbed dose derived from free radicals detected in enamel from extracted teeth from an individual can be measured using electron paramagnetic resonance (EPR), and is considered by many to be a component of biophysical or biological dosimetry. Confirming individual internal contamination by measuring radioactivity from radionuclides in biological samples (ie, urine, blood, feces, etc), which is commonly referred to as a “radiation bioassay,” and using radioactivity detectors to measure radionuclide contamination after clothing removal and washing are also commonly included in radiation exposure assessment. In-depth descriptions of radiation bioassays are beyond the scope of this chapter; hence, further discussions will be limited to recording of the type, amount, and body position of radionuclide contamination. Tissues and organs (ie, parotid gland, GI tissues, bone marrow, etc) exhibit cell and tissue injury at various times after radiation exposure, resulting in leakage of organ-specific components into blood that is often excreted in urine. The levels of these organ-specific biomarkers measured in blood plasma or urine have been used to augment clinical signs and symptoms of radiation dose and injury assessment. Proteomic biodosimetry and other selective emerging radiation exposure diagnostic technologies that show promise to provide triage and clinical biodosimetry applications will be described.<sup>2,3</sup>

Multiple parameter biological dosimetry is generally used to assess the severity of acute radiation syndrome or sickness (ARS), which is typically characterized into three phases in individuals suspected of exposure to life-threatening radiation doses: (1) initial or prodromal, (2) latent, and (3) manifest (or obvious) illness. The time to onset and severity for these three phases are influenced by radiation dose, quality (ie, gamma rays versus neutrons), dose rate, and the individual’s sensitivity to radiation (Table 6-1).

The primary purpose of early-response biodosimetry following suspected radiation overexposure is to rapidly provide first responders and medical providers scientifically sound diagnostic radiation injury and

dose assessment to support treatment decisions.<sup>4</sup> Assessing clinical signs and symptoms associated with the severity of organ-specific (ie, hematological, GI, cerebrovascular, and cutaneous) ARS, as developed and advocated by Professor TM Fliedner (Ulm, Germany), is essential for victim triage.<sup>5,6</sup> The risk of death from life-threatening radiation exposure depends on the level of medical care available (Figure 6-1 a).<sup>4</sup> The US Strategic National Stockpile Radiation Working Group recommended a treatment approach using both the organ-specific clinical signs and symptoms (based on the Medical Treatment Protocols for Radiation Accident Victims diagnostic system) and biological dosimetry (ie, time to onset of nausea and vomiting, decline in absolute lymphocyte counts over several hours to days after exposure, and appearance of chromosome aberrations [ie, dicentric and rings]).<sup>7</sup> In the case of a mass casualty radiation emergency, this working group recommended cytokine, antibiotic, and stem-cell transplant therapies (Figure 6-1 b). The working group also encouraged cytokine therapy to be initiated 24 hours after radiation exposure, based on the preclinical studies by MacVittie and colleagues.<sup>8</sup> This will likely necessitate an initial reliance on diagnostic information based on early bioindicators of radiation



**Figure 6-1.** (a) The effects of medical care levels on the risk of death as a function of radiation dose.

(b) Various medical treatment support approaches at dose windows recommended by the US Strategic National Stockpile Radiation Working Group.

Data source: Waselenko JK, MacVittie TJ, Blakely WF, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Working Group. *Ann Intern Med.* 2004;140(12):1037–1051.

TABLE 6-1

## ACUTE RADIATION SYNDROME IN HEALTHY ADULTS: WHOLE-BODY IRRADIATION FROM ACUTE PHOTON EQUIVALENT DOSES\*

		Survivability							
		Highly Survivable		Survivable to Lethal		Lethal			
		Degree of ARS							
		Mild		Moderate to Severe		Very Severe		Lethal	
		Dose Range							
Phase of Syndrome	Characteristic	0–100 cGy	100–200 cGy	200–600 cGy	600–800 cGy	800–3,000 cGy	> 3,000 cGy		
Prodromal phase	Vomiting:	NA	5%–50%	50%–100%	75%–100%	98%–100%	100%		
	Time of onset:		3–6 h	1–6 h	< 2 h	< 1 h	< 1 h		
	Duration:		< 24 h	< 24 h	< 48 h	< 48 h	< 48 h		
	Lymphocyte count (cells/mm <sup>3</sup> )	NA	< 1,400 at 4 days	< 1,400 at 48 h	< 1,000 at 24 h	< 800 at 24 h	NA		
	CNS function	No impairment		Routine task performance; cognitive impairment for 6–20 h	Simple and routine task performance; cognitive impairment for > 24 h	Transient incapacitation			
Latent phase	Duration, days	NA	7–15	0–21	0–2	0–2			
	Granulocytes (cells/mm <sup>3</sup> )	NA	> 2	1–2	≤ 0.5	≤ 0.1			
	Diarrhea	None		Rare	Appears on days 6–9	Appears on days 4–5			
	Epilation	None		Moderate, beginning on days 11–21	Complete earlier than day 11	Complete earlier than day 10			
	Latency period, days	NA	21–35	8–28	7 or less	None			
Manifest (obvious) illness	Signs and symptoms	None	Moderate leukopenia	Severe leukopenia, purpura, hemorrhage, pneumonia, hair loss after 300 rad (cGy)		Severe diarrhea, fever, electrolyte disturbance	Convulsions, ataxia, tremor, lethargy		
	Lymphocyte count (cells/mm <sup>3</sup> )	NA	0.8–1.0	0.1–0.8		0–0.1			
	Platelet count (cells/mm <sup>3</sup> )	NA	60–100	15–60		< 20			
	Time of onset	NA	> 2 wk	2 days–2 wk		0–2 days			
	Critical period	NA	None	4–6 wk		5–14 days	1–48 h		
Hospitalization	Principal organ system	None	Hematopoietic	Hematopoietic and gastrointestinal		Gastrointestinal (mucosal surfaces)	CNS		
	%	0%	< 5%	90%	100%	100%	100%		
Fatality	Duration		45–60 days	60–90 days	90+ days	2 wk	2 days		
	NA	0%	0%	0%–80%	80%–100%	98–100%			
Time of death	NA	NA	NA	3–12 wk		1–2 wk	1–2 days		

(Table 6-1 continues)

**Table 6-1** *continued*

ARS: acute radiation syndrome; CNS: central nervous system; NA: not applicable

\*Tabulated data for fatality incidence assumes no treatment.

Data source: Armed Forces Radiobiology Research Institute. *AFRRI Pocket Guide: Emergency Radiation Medicine Response*. Bethesda, MD: AFRRI; September 2008. [www.usuhs.mil/afri/outreach/pdf/AFRRI-Pocket-Guide.pdf](http://www.usuhs.mil/afri/outreach/pdf/AFRRI-Pocket-Guide.pdf). Accessed March 23, 2011.

dose, which will then be replaced by bioindicators of the severity of ARS response as the clinical case evolves.

The accepted generic multiparameter and early-response approach is described in Exhibit 6-1.<sup>19</sup> Effective medical management of a suspected acute radiation overexposure incident necessitates recording dynamic medical data, measuring appropriate radiation bioassays, and estimating dose from dosimeters and radioactivity assessments to provide diagnostic information to the treating physician and a dose assessment for personnel radiation protection records.

An additional purpose for biodosimetry is to

support a quality radiation protection program by documenting the levels of radiation exposure for individuals suspected or known to be overexposed to radiation. Historically, a major activity in these effects is retrospective biodosimetry, which entails an assessment of radiation exposure long (ie, months to years) after the exposure. In these cases, dose assessment by biodosimetry methods has typically been limited to use of persistent radiation biomarkers supplemented by alternative physical dose reconstruction methodologies.<sup>10</sup> Dose assessments by retrospective dosimetry are commonly used to contribute to radiation epidemiology studies.

### MEDICAL RECORDING

Medical recording is essential for effectively diagnosing and managing radiation at the incident scene as well as during transport to and while at the medical treatment facility. Medical recording guidance concerning radiation casualty management is available from the International Atomic Energy Agency.<sup>11</sup> The Armed Forces Radiobiology Research Institute (AFRRI) has approached this requirement using medical recording forms in annotatable portable document format (PDF) and medical recording and dose-assessment software (Figure 6-2).

Medical recording for radiation incidents should be consistent with an “all hazards” approach used by first responders. AFRRI’s Adult/Pediatric Field Medical Record (AFRRI Form 330) provides a medical record template in a convenient, 1-page form for gathering emergency medical information in the field. It is applicable to both adult and pediatric cases (Attachment 1). The AFRRI Biodosimetry Worksheet (AFRRI Form 331) represents a comprehensive data entry worksheet, recently expanded from 4 to 6 pages to accommodate a modified version of the Medical Treatment Protocols

#### EXHIBIT 6-1

#### BIODOSIMETRY: GENERAL GUIDANCE FOR EARLY-PHASE RESPONSE\*

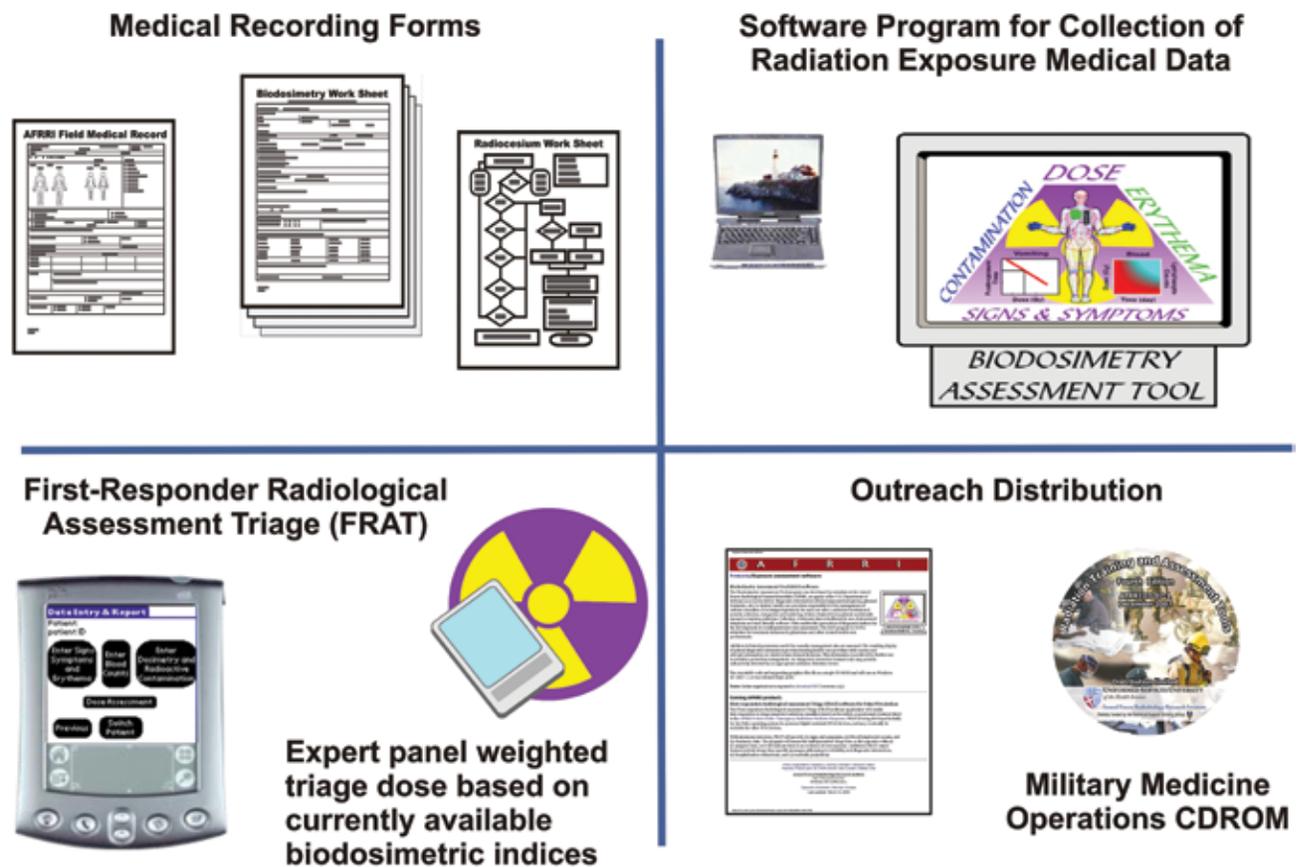
##### Actions needed in suspected overexposures:

- Perform measurements and bioassay, if appropriate, to determine radioactivity contamination.
- Observe and record prodromal signs and symptoms.
- Obtain complete blood count with white blood cell differential immediately, then every 6 hours for 2 to 3 days, and then twice a day for 4 days.
- Record physical dosimetry measurements, if available.
- Contact a qualified laboratory to evaluate performance of chromosome aberration cytogenetic bioassay for dose assessment.
- Consider other opportunistic dosimetry approaches, as available.

\*Lifesaving measures should be given higher priority than biodosimetry assessment. The sequence of actions can be modified depending on the radiation exposure scenario.

# Biodosimetry Tools Supporting Medical Recording

[www.afrrri.usuhs.mil/outreach/biodostools.htm](http://www.afrrri.usuhs.mil/outreach/biodostools.htm)



**Figure 6-2.** Armed Forces Radiobiology Research Institute’s biological dosimetry tools supporting medical recording. Courtesy of: Armed Forces Radiobiology Research Institute, Bethesda, MD.

for Radiation Accident Victims ARS severity scoring system. It provides a place to record the facts about a case of radiation exposure, including the source and type of radiation, the extent of exposure, relevant biodosimetry diagnostic information, and the nature of the resulting injuries. The form is applicable to both adult and pediatric cases (Attachment 2).

The Biodosimetry Assessment Tool (BAT) program (version 1.0) for Windows XP (Microsoft Corporation, Redmond, WA) was developed by AFRRRI scientists as a tool to record and deliver diagnostic information (clinical signs and symptoms, physical dosimetry, etc) to healthcare providers responsible for managing radiation casualties.<sup>1,12-15</sup> It is designed primarily for early use after a radiation incident and permits collection, integration, and archiving of data obtained from patients suspected or known to be exposed to ionizing radiation. Relevant data is collected via struc-

tured templates and user-friendly software, enabling the generation of diagnostic indices for developing a multiparameter dose assessment. The BAT program is not a substitute for treatment decisions by physicians and other trained healthcare professionals. Additional clinical parameters (ie, infection, treatments, etc) useful for casualty management are also assessed. The resulting display of patient diagnostic information provides treating healthcare providers with concise and relevant information on which to base clinical decisions. This information can be archived for further use in radiation protection management. An integrated, interactive, human body map makes it possible to record radionuclides detected by an appropriate radiation-detection device. BAT is distributed online upon review of a download request application (available at <http://www.afrrri.usuhs.mil>). An alternative version of BAT (eBAT) with more secure data handling is distributed

by Medical Communications for Combat Casualty Care ([www.mc4.army.mil/index.asp](http://www.mc4.army.mil/index.asp)).

The First-Responders Radiological Assessment Triage (FRAT) program enables first responders to triage suspected radiation casualties based on the initial, or prodromal, features listed in the *AFRRI Pocket Guide: Emergency Radiation Medicine Response*.<sup>16,17</sup> FRAT is being developed initially for the Palm operating system (Palm, Inc, Sunnyvale, CA) and may eventually be available for other devices using other operating systems (eg, Windows). With minimum

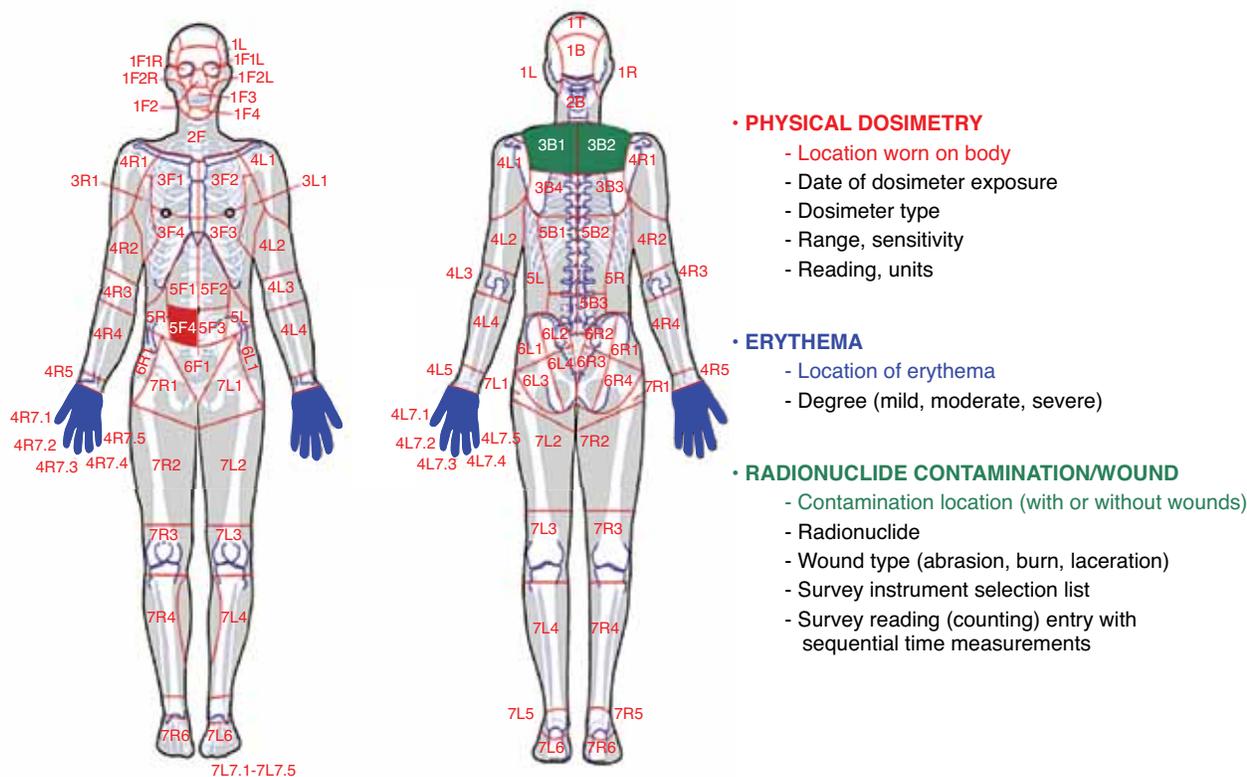
text entry, FRAT will record signs and symptoms, blood lymphocyte counts, and dosimetry data. The program will assess multiparameter triage dose or exposure without an assigned dose, or it will indicate that there is no evidence of overexposure. Additional FRAT output features include triage dose-specific messages addressing reliability and diagnostic information, hospitalization estimations, and mortality projections. The FRAT utility provides a triage dose estimate based on multiple-parameter, weighted, dose-assessment indices.

### INTERNAL CONTAMINATION AND PHYSICAL DOSIMETRY

An individual's location relative to a radiation source, as well as internal contamination of radionuclides, if applicable, can contribute to radiation exposure assessment. The location of radionuclide contamination on the body, internal contamination information, dose estimation based on location, and dose based on personal dosimeters, if available, should be recorded by first responders and medical personnel

(Figure 6-3).<sup>1,9</sup> The BAT application provides templates for recording these and other relevant parameters (eg, location and activity of radiation source, patient location relative to radiation source, etc) that can contribute to medical management and dose reconstruction. Metallic (or other) fragment samples should be collected for isotope classification, as appropriate, for identifying the radiation exposure scenario. In addition, biologi-

#### RECORD BODY LOCATION\*



**Figure 6-3.** Illustration of a record and recommended data collection for body location of physical dosimeters, presence of radiation-induced erythema, and radionuclide contamination in an exposed individual.

cal samples (ie, urinalysis, fecal, wound, swabs from body orifices) should also be collected for determining the committed dose. Protocols for biological sample collection for radiation bioassays and information for estimating dose based on location are described by

Alexander and colleagues.<sup>9</sup> AFRRRI's FRAT application uses information from physical dosimeters and radionuclide contamination that remains after clothing removal and washing as evidence for radiation exposure in a triage dose assessment algorithm.

### PRODROMAL SIGNS AND SYMPTOMS

The prodromal response to exposure to ionizing radiation is characterized by a dose-dependent expression of a constellation of signs and symptoms, including the following:

- nausea,
- vomiting,
- headache,
- fever,
- tachycardia,
- fatigue,
- weakness,
- abdominal pain,
- parotid pain, and
- erythema.<sup>18</sup>

The time to onset and severity of early prodromal phase signs and symptoms can provide some valuable information regarding the absorbed "dose range." The FRAT application integrates these early-phase radioreponses to provide a triage dose assessment. Progressive increases in radiation dose result in an increased percentage of both the incidence and the constellation of prodromal signs and symptoms.

The appearance of acute symptoms, such as vomiting, is directly dependent on the radiation dose to an overexposed individual and contributes to the multiparameter diagnostic index (Table 6-2) used for assessing dose.<sup>18</sup> Data used to develop algorithms for dose predictions based on onset of vomiting used in the BAT and FRAT applications were drawn from the work of Anno et al<sup>18</sup> and Goans et al.<sup>19-21</sup> Following photon and criticality incident exposures, the BAT program can be used to record prodromal symptoms and assess dose-prediction models for time to onset of vomiting.<sup>12-14</sup> An

acute photon exposure dose of 2 Gy would cause about 50% of individuals to exhibit emesis approximately 4.6 hours post-irradiation. However, since potential confounders (influenza epidemic, etc) can also induce similar symptoms, caution is warranted when using selective prodromal symptoms alone to assess dose and efficiently treat the radiation incident victim. For example, the incidence of psychogenic vomiting would likely be elevated during stressful events, such as a radiological mass casualty incident. Prodromal symptoms cannot be ignored but should be recorded and medically managed.

The location and time course of radiation-induced cutaneous injury should also be recorded (see Figure 6-3). Reddening of the skin, or initial erythema, is generally seen within a few hours to a few days following exposure to a high radiation dose (> 2 Gy) and lasts for only a day or two. Diagnostic information about local partial versus whole-body injury can be gleaned by observing if selected body regions exhibit erythema; these observations can later help define the boundary of the radiation exposure area when skin grafts are necessary. The AFRRRI Biodosimetry Worksheet (Attachment 2) and BAT program provide data templates for this purpose. The time course for the skin's erythema response to radiation is biphasic. This type of skin reaction is largely due to capillary dilation caused by the release of histamine-like substances. Erythema increases during the first week following exposure and then generally subsides during the second week. It may return 2 to 3 weeks after the initial insult and last up to 30 days, and additional changes, such as desquamation, bullae formation, or even skin sloughing, may follow, all of which make even a crude estimation of radiation dose problematic.

### HEMATOLOGICAL BIOINDICATORS

Hematological responses are early response biomarkers for radiation dose assessment. Data derived from radiation accidents registries contribute to the development of dose and injury severity assessment models.<sup>5,18,19,22-25</sup> Fliedner advocates the use of blood cell changes after whole-body radiation exposures as reliable bioindicators of injury and critical aids to planning therapeutic treatments.<sup>5,22</sup> Immediately following

exposure, a complete blood cell count with white-cell differential should be obtained, then repeated three times a day for the next 2 to 3 days, and then twice a day for the following 3 to 6 days. The combined use of early-phase lymphocyte depletion, rise and then fall in neutrophils, and increases in the ratio of neutrophils to lymphocytes provides a hematology profile to identify individuals with potentially severe bone marrow ARS.

**TABLE 6-2**  
**BIODOSIMETRY BASED ON ACUTE PHOTON-EQUIVALENT EXPOSURES\***

Dose Estimate (Gy)	Individuals Who Vomited (%) <sup>†</sup>	Time to Onset of Vomiting (h)	Absolute Lymphocyte Count ( $\times 10^9/L$ ) <sup>‡</sup> (day)						Lymphocyte Depletion Rate (rate constant)	Relative Increase in Serum Amylase Activity at 1 Day Compared to Normal	Number of Dicentrics <sup>§</sup>	
			0.5	1	2	4	6	8			Per 50 Meta-phases	Per 1,000 Meta-phases
0	NA	NA	<b>2.45</b>	<b>2.45</b>	<b>2.45</b>	<b>2.45</b>	<b>2.45</b>	<b>2.45</b>	NA	1	0.05–0.1	1–2
1	19	>10.0	<b>2.30</b>	<b>2.16</b>	<b>1.90</b>	<b>1.48</b>	1.15	0.89	0.126	2	4	88
2	35	4.63	<b>2.16</b>	<b>1.90</b>	<b>1.48</b>	0.89	0.54	0.33	0.252	4	12	234
3	54	2.62	<b>2.03</b>	<b>1.68</b>	1.15	0.54	0.25	0.12	0.378	6	22	439
4	72	1.74	<b>1.90</b>	<b>1.48</b>	0.89	0.33	0.12	0.044	0.504	10	35	703
5	86	1.27	<b>1.79</b>	1.31	0.69	0.20	0.06	0.020	0.63	13	51	1034
6	94	0.99	<b>1.68</b>	1.15	0.54	0.12	0.03	0.006	0.756	15	ND	ND
7	98	0.79	<b>1.58</b>	1.01	0.42	0.072	0.012	0.002	0.881	16.5	ND	ND
8	99	0.66	<b>1.48</b>	0.89	0.33	0.044	0.006	< .001	1.01	17.5	ND	ND
9	100	0.56	1.39	0.79	0.25	0.030	0.003	< .001	1.13	18	ND	ND
10	100	0.48	1.31	0.70	0.20	0.020	0.001	< .001	1.26	18.5	ND	ND

\*Depicted above are the most useful elements of biodosimetry. Dose range is based on acute photon-equivalent exposures. Two or more determinations of blood lymphocyte counts are made to predict a rate constant, which is used to estimate exposure dose. The final column represents the current “gold standard,” which requires several days before results are known. Colony-stimulating factor therapy should be initiated when onset of vomiting, lymphocyte depletion kinetics, 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.

<sup>†</sup>Cumulative percentage of individuals with vomiting.

<sup>‡</sup>Normal range:  $1.4\text{--}3.5 \times 10^9/L$ . Numbers in bold fall within this range.

<sup>§</sup>Number of dicentric chromosomes in human peripheral blood.

NA: not applicable; ND: not done

Data sources: (1) Blakely WF. Early biodosimetry response: recommendations for mass-casualty radiation accidents and terrorism. Paper presented at: Refresher Course for the 12th International Congress of the International Radiation Protection Association; October 19–24, 2008; Buenos Aires, Argentina. (2) Waselenko JK, MacVittie TJ, Blakely WF, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Working Group. *Ann Intern Med.* 2004;140(12):1037–1051. (3) Sandgren DJ, Salter CA, Levine IH, Ross JA, Lillis-Hearne PK, Blakely WF. Biodosimetry Assessment Tool (BAT) software-dose prediction algorithm. *Health Phys.* 2010;99(Suppl 5):S171–S183. (4) Waselenko JK, MacVittie TJ, Blakely WF, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Working Group. *Ann Intern Med.* 2004;140(12):1037–1051. (5) Chen IW, Kereiakes JG, Silberstein EB, Aron BS, Saenger EL. Radiation-induced change in serum and urinary amylase levels in man. *Radiat Res.* 1973;54:141–151.

At later times (> 10 days) after radiation exposure, progressive depletions of peripheral blood platelets and neutrophil counts below baseline levels are indicative of a higher radiation dose and severity of injury.

Lymphocyte cell counts and lymphocyte depletion kinetics can provide early-phase dose assessment predictions that fall in the equivalent photon dose range of 1 to 10 Gy for up to 10 days after radiation exposure (see Table 6-2). Decline of approximately 50% in peripheral blood lymphocyte counts over 12 hours that also fall below normal values ( $1.4 \times 10^9/L$ ) is indicative of a potential severe

radiation overexposure.<sup>47</sup> Caution is warranted in the use of lymphocyte cell counts that fall in the normal range for radiation dose predictions. Goans and colleagues introduced lymphocyte-depletion kinetic models for dose estimates based on human radiation accident registry data for whole-body, acute gamma exposures and, more recently, for criticality accidents.<sup>19–21</sup> The BAT program permits the recording of peripheral blood lymphocyte counts and then converts them into dose predictions using lymphocyte depletion kinetic models based on consensus data from radiation accidents registries.<sup>18–21,23,24</sup>

Fliedner and colleagues reported consensus results for the early rise (granulocytosis) and subsequent fall (granulocytopenia) in peripheral blood granulocyte cell counts following exposure to ionizing radiation.<sup>5,22,25</sup> Recently Zhang and colleagues proposed monitoring the ratio of neutrophils (major subset of granulocytes) to lymphocytes early after radiation exposure as a more practical, multifactorial, prognostic radiation indicator.<sup>26</sup> These hematological changes are proposed as prognostic indices to identify severely irradiated individuals indicative of partial or complete failure of the blood-forming system.<sup>5,7</sup> Decreased normal peripheral blood lymphocyte and neutrophil baseline counts, however, are seen in certain populations (eg, people of African and Middle Eastern descent).<sup>27,28</sup> Diagnostic use of hematopoietic cell count for radiation

exposure assessment requires comparison of results with appropriate baseline level controls.

In a radiological mass-casualty incident, it may not be practical to perform repeated serial blood cell counts on multiple individuals. In this case it may be difficult to catch the early transitory rise in neutrophils (or granulocytes) early after radiation exposure. As initially recommended by Zhang and colleagues (based on the analysis of human accident registry results and later confirmed by Blakely and colleagues using nonhuman, primate radiation models), the early-phase decrease in lymphocytes (ie, 12 hours to 10 days after irradiation) and increase in the ratio of neutrophils to lymphocytes (ie, 1 to 3 days after irradiation) early after radiation exposure can aid in identifying individuals with life-threatening radiation overexposures.<sup>26,29,30</sup>

### EMERGING TRIAGE DIAGNOSTIC APPROACHES

Several provisional and emerging approaches have been considered as methods to provide triage, clinical, and definitive dose assessment. For a review of these and other established dose assessment methods, see reports by Blakely et al,<sup>1</sup> Turteltaub et al,<sup>3</sup> and Alexander et al.<sup>9</sup>

EPR-based detection of free radicals is a well accepted and validated method for measuring dose to dental enamel from tooth biopsy and has recently been extended to measure absorbed dose from teeth *in vivo* and nail clippings *ex vivo*.<sup>2,9,31,32</sup> Provisional protocols for sample collection of nail clippings are established.<sup>9</sup> There are ongoing efforts to establish diagnostic technologies for *in-vivo* EPR from teeth.<sup>9</sup> Biophysical dose assessment using *in-vivo* EPR from teeth, along with *ex-vivo* EPR from nail-clipping samples from the extremities would contribute to mapping partial-body exposures and allow an estimate of regional (head, extremities) radiation exposure, and could point to bone-marrow sparing.<sup>33</sup>

Blood biochemical markers of radiation exposure have also been advocated for use in early triage of radiation casualties.<sup>17,34-36</sup> An increase in serum amylase activity (hyperamylasemia) from the irradiation of salivary tissue has been proposed as a biochemical measure of early radiation effects.<sup>37,38</sup> Several studies have also advocated its use as a candidate biochemical dosimeter in humans.<sup>17,39-43</sup> A few hours after irradiation injury, cells in the salivary glands show acute inflammation and degenerative changes resulting in increases in serum amylase activity. Histochemical, isozyme analysis, and partial-body exposure studies confirm that the increase in serum amylase activity originated from the salivary glands. Serum amylase activity increases occur early after head and neck irradiation of humans and

generally show peak values between 18 and 30 hours after exposure, returning to normal levels within a few days.<sup>42,44</sup> Sigmoidal dose-dependent increases in early (1 day) hyperamylasemia are supported by radioiodine therapy, radiotherapy, and from limited data from three individuals exposed in a criticality accident.<sup>37,39-47</sup> Significant interindividual variations are reported in dose-response studies, which represent a potential major confounder for use of serum amylase activity alone as a reliable biodosimeter.<sup>38,44,46,47</sup> This interindividual variation in biochemical response is not unexpected, since it is well known that the radiation level causing irreversible failure of the hematopoietic system varies among individuals and may reflect genetic and physiological differences and relative differences in the radiosensitivity of hematopoietic stem and progenitor cells as well as radiation exposure parameters (ie, partial-body exposures, shielding, dose rate, etc).<sup>48,49</sup>

Radiation causes injury to various tissues and organs, resulting in time- and dose-dependent increases in tissue- and organ-specific proteins in blood. These blood plasma proteins are bioindicators for radiation injury of relevant ARS organ systems (ie, bone marrow, GI system) as well as early bioindicators of absorbed dose (Tables 6-3 and 6-4). Ideally, a panel of radiation protein biomarkers from distinctly different pathways and tissue sources would provide the necessary radiation specificity and sensitivity for clinical and definitive radiation diagnosis and to overcome potential confounders (ie, elevated amylase activity due to salivary gland infection; elevated C-reactive protein due to chronic inflammation, including rheumatoid conditions, autoimmune diseases, and heart attacks; and increases in neutrophil counts due to severe septicemia).

TABLE 6-3

CANDIDATE RADIATION BIOMARKERS AND FUNCTIONAL TESTS FROM VARIOUS TISSUE SYSTEM AND ORGANS

Tissue System/Organ	Candidate Radiation Biomarker	Candidate Radiation Bioindicator or Functional Test	Radiation Pathology
<b>Gastrointestinal/Digestive</b>			
Parotid salivary gland	Amylase activity	↑ serum or urinary amylase activity	Mucositis <sup>1-5</sup>
Small intestine	Citrulline, neurotension, and gastrin hormones	↓ serum or plasma citrulline, neurotensin, or gastrin; ↑ sugar concentration ratios using dual-sugar permeability test measured in serum	GI ARS subsyndrome <sup>6-9</sup>
Liver	CRP, SAA; oxysterol 7a-hydroxycholesterol	↑ serum or plasma CRP or SAA; ↑ plasma oxysterol 7a-hydroxycholesterol	ARS subsyndrome; hepatic tissue radiation injury <sup>3,10-18</sup>
<b>Hemopoietic</b>			
Bone marrow	Flt-3L, IL-6, G-CSF	↑ serum or plasma Flt-3L	Bone marrow ARS subsyndrome <sup>6,16,18-23</sup>
<b>Cutaneous</b>			
Skin	Cytokines (IL-1, IL-6, tumor necrosis factor, GM-CSF, TGF-β, intracellular adhesion molecule, MMP)	↑ IL-1, IL-6, GM-CSF, TGF-β, intracellular adhesion molecule, and MMP measured from skin tissues	Cutaneous ARS subsyndrome <sup>24-28</sup>
<b>Respiratory</b>			
Lung	Oxysterol 27-hydrocholesterol	↑ plasma oxysterol 27-hydrocholesterol	Respiratory ARS subsyndrome <sup>15</sup>
<b>Cerebrovascular/Central Nervous</b>			
All	Oxysteril 24S-hydroxycholesterol	↑ plasma oxysteril 24S-hydroxycholesterol	Cerebrovascular ARS subsyndrome <sup>15</sup>

ARS: acute radiation syndrome; CRP: C-reactive protein; Flt-3L: FMS-like tyrosine kinase 3 ligand; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; GI: gastrointestinal; IL: interleukin; MMP: matrix metalloproteinases; SAA: serum amyloid A; TGF-β: transforming growth factor β

(1) Blakely WF, King GL, Ossetrova NI, Port M. Molecular biomarkers of acute radiation syndrome and radiation injury. In: Blakely WF, Duffy F, Edwards K, Janiak MK, eds. *Radiation Bioeffects and Countermeasures*. North Atlantic Treaty Organization, Research and Technology Organization, Human Factors and Medicine: Neuilly-sur-Seine, France; 2011. Chapter 5. Technical Report-099, RTO-TR-HFM-099, AC/323(HFM-099) TP/356. Available at: <http://www.rto.nato.int>. (2) Chen IW, Kereiakes JG, Silberstein EB, Aron BS, Saenger EL. Radiation-induced change in serum and urinary amylase levels in man. *Radiat Res*. 1973;54:141-151. (3) Blakely WF, Ossetrova NI, Manglapus GL, et al. Amylase and blood cell-count hematological radiation-injury biomarkers in a rhesus monkey radiation model—use of multiparameter and integrated biological dosimetry. *Radiat Meas*. 2007;42(6-7):1164-1170. (4) Blakely WF, Ossetrova NI, Whitnall MH, et al. Multiple parameter radiation injury assessment using a nonhuman primate radiation model—biodosimetry applications. *Health Phys*. 2010;98:153-159. (5) Hofmann R, Schreiber GA, Willich N, Westhaus R, Bögi KW. Increased serum amylase in patients as a probable bioindicator for radiation exposure. *Strahlenther Onkol*. 1990;166(10):688-695. (6) Becciolini A, Porciani S, Lanini A, Balzi M, Faroani P. Proposal for biochemical dosimeter for prolonged space flights. *Phys Med*. 2001;17(Suppl 1):185-186. (7) Bertho JM, Roy L, Souidi M, et al. New biological indicators to evaluate and monitor radiation-induced damage: an accident case report. *Radiat Res*. 2008;169:543-550. (8) Lutgens LC, Deutz NE, Gueulette J, et al. Citrulline: a physiologic marker enabling quantitation and monitoring of epithelial radiation-induced small bowel damage. *Int J Radiat Oncol Biol Phys*. 2003;57:1067-1074. (9) Lutgens LC, Deutz N, Granzier-Peters M. Plasma citrulline concentration: a surrogate end point for radiation-induced mucosal atrophy of the small bowel. A feasibility study in 23 patients. *Int J Radiat Oncol Biol Phys*. 2004;60:275-285. (10)

(Table 6-3 continues)

Table 6-3 continued

Vigneulle RM, Rao S, Fasano A, MacVittie TJ. Structural and functional alterations of the gastrointestinal tract following radiation-induced injury in the rhesus monkey. *Dig Dis Sci*. 2002;47:1480–1491. (11) Dublneau I, Dudoignon N, Monti P, et al. Screening of a large panel of gastrointestinal peptide plasma levels is not adapted for the evaluation of digestive damage following irradiation. *Can J Physiol Pharmacol*. 2004;82:103–113. (12) Mal'tsev VN, Strel'nikov VA, Ivanov AA. C-reactive protein in the blood serum as an indicator of the severity of radiation lesion [in Russian]. *Dokl Akad Nauk SSSR*. 1978;239:750–752. (13) Mal'tsev VN, Ivanov AA, Mikhaïlov VF, Mazurik VK. The individual prognosis of the gravity and of the outcome of acute radiation disease based on immunological indexes [in Russian]. *Radiats Biol Radioecol*. 2006;46(2):152–158. (14) Goltry KL, Epperly MW, Greenberger JS. Induction of serum amyloid A inflammatory response genes in irradiated bone marrow cells. *Radiat Res*. 1998;149:570–578. (15) Koc M, Taysi S, Sezen O, Bakan N. Levels of some acute-phase proteins in the serum of patients with cancer during radiotherapy. *Biol Pharm Bull*. 2003;26(10):1494–1497. (16) Roy L, Berthro JM, Souidi M, Vozenin MC, Voisin P, Benderitter M. Biochemical approach to prediction of multiple organ dysfunction syndrome. *BJR Suppl*. 2005;27:146–151. (17) Ossetrova NI, Farese AM, MacVittie TJ, Manglapus GL, Blakely WF. The use of discriminant analysis for evaluation of early-response multiple biomarkers of radiation exposure using non-human primate 6-Gy whole-body radiation model. *Radiat Meas*. 2007;42:1158–1163. (18) Ossetrova NI, Sandgren DJ, Gallego S, Blakely WF. Combined approach of hematological biomarkers and plasma protein SAA for improvement of radiation dose assessment in triage biodosimetry applications. *Health Phys*. 2010;98:204–208. (19) Ossetrova NI, Blakely WF. Multiple blood-proteins approach for early-response exposure assessment using an in vivo murine radiation model. *Int J Radiat Biol*. 2009;85(10):837–850. (20) Berthro JM, Roy L. A rapid multiparametric method for victim triage in cases of accidental protracted irradiation or delayed analysis. *Br J Radiol*. 2009;82:764–770. (21) Berthro JM, Demarquay C, Frick J, et al. Level of Flt3-ligand in plasma: a possible new bio-indicator for radiation-induced aplasia. *Int J Radiat Biol*. 2001;77(6):703–712. (22) Beetz A, Messer G, Opperl T, van Beuningen D, Peter RU, Kind P. Induction of interleukin 6 by ionizing radiation in a human epithelial cell line: control by corticosteroids. *Int J Radiat Biol*. 1997;72:3–43. (23) Gartel AL, Tyner AL. The role of the cyclin-dependent kinase inhibitor p21 in apoptosis. *Mol Cancer Ther*. 2002;1:639–649. (24) Bellido T, O'Brien CA, Roberson PK, Manolagas SC. Transcriptional activation of the p21 (WAF1, CIP1, SDI1) gene by interleukin-6 type cytokines. A prerequisite for their pro-differentiating and anti-apoptotic effects on human osteoblastic cells. *J Biol Chem*. 1998;273:21137–21144. (25) Martin M, Vozenin MC, Gault N, Crechet F, Pfarr CM, Lefaix JL. Coactivation of AP-1 activity and TGF- $\beta$ 1 gene expression in the stress response of normal skin cells to ionizing radiation. *Oncogene*. 1997;15:981–989. (26) Ulrich D, Noah EM, von Heimburg D, Pallua N. TIMP-1, MMP-2, MMP-9, and PIIINP as serum markers for skin fibrosis in patients following severe burn trauma. *Plast Reconstr Surg*. 2003;111:1423–1431. (27) Liu W, Ding I, Chen K, et al. Interleukin 1 $\beta$ (IL1B) signaling is a critical component of radiation-induced skin fibrosis. *Radiat Res*. 2006;165:181–191. (28) Müller K, Meineke V. Radiation-induced alterations in cytokine production by skin cells. *Exp Hematol*. 2007;35:96–104. (29) Guipaud O, Holler V, Buard V, et al. Time-course analysis of mouse serum proteome changes following exposure of the skin to ionizing radiation. *Proteomics*. 2007;7:3992–4002.

TABLE 6-4

## SELECT RADIATION-RESPONSIVE, BLOOD-BASED, PROTEOMIC, METABOLOMIC, AND HEMATOLOGIC BIOMARKERS

Proposed Blood or Serum Biomarker	Pathways	Dose Range (Gy)				Time Window for Meaningful Diagnostics
		Rodent Studies	Nonhuman Primate Studies	Human Radiation Therapy	Human Radiation Accidents	
Salivary $\alpha$ -amylase activity	Parotid gland tissue injury	NA	0–8.5 Gy	0.5–10 Gy	3.5, 8, and 18 Gy (Tokaimura)	12–36 h; peaks at 24 h <sup>1–5</sup>
IL-6, G-CSF	Immunostimulatory effects on bone marrow cells	1–7 Gy	6.5 Gy	NA	1–10 Gy	Phase 1: 4–48 h Phase 2: 3–8 d <sup>6–11</sup>
Flt-3 ligand	Bone marrow aplasia	1–7 Gy	1–14 Gy	NA	0.25–4.5 Gy	24 h–10 d <sup>12,13</sup>
CRP, SAA	Acute phase reaction	1–7 Gy (SAA)	1–14 Gy (CRP)	1–20 Gy (CRP)	1–10 Gy (CRP)	Phase 1: 6 h–4 d Phase 2: 5–14 d <sup>2,6–8,14–17</sup>
Citrulline	Small bowel epithelial injury	1–14 Gy	Not done	1–20 Gy (2-Gy daily fractions)	~ 4.5 Gy	> 24 h <sup>12,17,18</sup>
Lymphocytes, neutrophils, and ratio of neutrophils to lymphocytes	Hematopoietic tissue injury	1–7 Gy	1–8.5 Gy	1–20 Gy	0–30 Gy	2 h–8 d <sup>7,19–22</sup>

(Table 6-4 continues)

**Table 6-4** continued

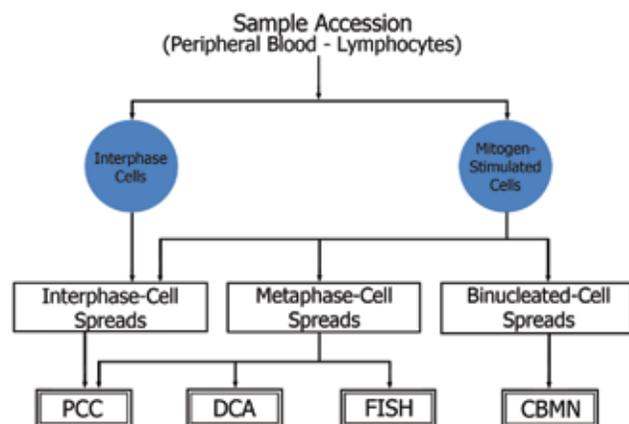
CRP: C-reactive protein; Flt-3: FMS-like tyrosine kinase 3; G-CSF: granulocyte colony-stimulating factor; IL: interleukin; NA: not applicable; SAA: serum amyloid A

(1) Blakely WF, Ossetrova NI, Manglapus GL, et al. Amylase and blood cell-count hematological radiation-injury biomarkers in a rhesus monkey radiation model—use of multiparameter and integrated biological dosimetry. *Radiat Meas.* 2007;42(6–7):1164–1170. (2) Hofmann R, Schreiber GA, Willich N, Westhaus R, Bögi KW. Increased serum amylase in patients as a probable bioindicator for radiation exposure. *Strahlenther Onkol.* 1990;166(10):688–695. (3) Dubray B, Girinski T, Thames HD, et al. Post-irradiation hyperamylasemia as a biological dosimetry. *Radiother Oncol.* 1992;24(1):21–26. (4) Becciolini A, Porciani S, Lanini A, Balzi M, Faroani P. Proposal for biochemical dosimeter for prolonged space flights. *Phys Med.* 2001;17(Suppl 1):185–186. (5) Ossetrova NI, Farese AM, MacVittie TJ, Manglapus GL, Blakely WF. The use of discriminant analysis for evaluation of early-response multiple biomarkers of radiation exposure using non-human primate 6-Gy whole-body radiation model. *Radiat Meas.* 2007;42:1158–1163. (6) Ossetrova NI, Sandgren DJ, Gallego S, Blakely WF. Combined approach of hematological biomarkers and plasma protein SAA for improvement of radiation dose assessment in triage biodosimetry applications. *Health Phys.* 2010;98:204–208. (7) Ossetrova NI, Blakely WF. Multiple blood-proteins approach for early-response exposure assessment using an in vivo murine radiation model. *Int J Radiat Biol.* 2009;85(10):837–850. (8) Beetz A, Messer G, Oettel T, van Beuningen D, Peter RU, Kind P. Induction of interleukin 6 by ionizing radiation in a human epithelial cell line: control by corticosteroids. *Int J Radiat Biol.* 1997;72:3–43. (9) Gartel AL, Tyner AL. The role of the cyclin-dependent kinase inhibitor p21 in apoptosis. *Mol Cancer Ther.* 2002;1:639–649. (10) Bellido T, O'Brien CA, Roberson PK, Manolagas SC. Transcriptional activation of the p21 (WAF1, CIP1, SDI1) gene by interleukin-6 type cytokines. A prerequisite for their pro-differentiating and anti-apoptotic effects on human osteoblastic cells. *J Biol Chem.* 1998;273:21137–21144. (11) Bertho JM, Roy L, Souidi M, et al. New biological indicators to evaluate and monitor radiation-induced damage: an accident case report. *Radiat Res.* 2008;169:543–550. (12) Bertho JM, Demarquay C, Frick J, et al. Level of Flt3-ligand in plasma: a possible new bio-indicator for radiation-induced aplasia. *Int J Radiat Biol.* 2001;77(6):703–712. (13) Blakely WF, Ossetrova NI, Whitnall MH, et al. Multiple parameter radiation injury assessment using a nonhuman primate radiation model—biodosimetry applications. *Health Phys.* 2010;98:153–159. (14) Mal'tsev VN, Strel'nikov VA, Ivanov AA. C-reactive protein in the blood serum as an indicator of the severity of radiation lesion [in Russian]. *Dokl Akad Nauk SSSR.* 1978;239:750–752. (15) Mal'tsev VN, Ivanov AA, Mikhaïlov VF, Mazurik VK. The individual prognosis of the gravity and of the outcome of acute radiation disease based on immunological indexes [in Russian]. *Radiats Biol Radioecol.* 2006;46(2):152–158. (16) Goltry KL, Epperly MW, Greenberger JS. Induction of serum amyloid A inflammatory response genes in irradiated bone marrow cells. *Radiat Res.* 1998;149:570–578. (17) Lutgens LC, Deutz NE, Gueulette J, et al. Citrulline: a physiologic marker enabling quantitation and monitoring of epithelial radiation-induced small bowel damage. *Int J Radiat Oncol Biol Phys.* 2003;57:1067–1074. (18) Lutgens LC, Deutz N, Granzier-Peeters M. Plasma citrulline concentration: a surrogate end point for radiation-induced mucosal atrophy of the small bowel. A feasibility study in 23 patients. *Int J Radiat Oncol Biol Phys.* 2004;60:275–285. (19) Blakely WF, Salter CA, Prasanna PG. Early-response biological dosimetry—recommended countermeasure enhancements for mass-casualty radiological incidents and terrorism. *Health Phys.* 2005;89(5):494–504. (20) Blakely WF, Ossetrova NI, Manglapus GL, et al. Amylase and blood cell-count hematological radiation-injury biomarkers in a rhesus monkey radiation model—use of multiparameter and integrated biological dosimetry. *Radiat Meas.* 2007;42(6–7):1164–1170. (21) Goans RE, Holloway EC, Berger ME, Ricks RC. Early dose assessment following severe radiation accidents. *Health Phys.* 1997;72(4):513–518. (22) Gus'kova AK, Baranov AE, Gusev IA. Acute radiation sickness: underlying principles and assessment. In: Gusev AE, Gus'kova AK, Mettler FA Jr, eds. *Medical Management of Radiation Accidents.* Boca Raton, FL: CRC Press; 2001: 33–51.

Data source: Blakely WF, King GL, Ossetrova NI, Port M. Molecular biomarkers of acute radiation syndrome and radiation injury. In: Blakely WF, Duffy F, Edwards K, Janiak MK, eds. *Radiation Bioeffects and Countermeasures.* North Atlantic Treaty Organization, Research and Technology Organization, Human Factors and Medicine: Neuilly-sur-Seine, France; 2011. Chapter 5. Technical Report-099, RTO-TR-HFM-099, AC/323(HFM-099)TP/356. Available at: <http://www.rto.nato.int>.

### CYTOGENETIC BIODOSIMETRY

Multiple cytogenetic chromosome aberration assays (Figure 6-4) are useful for biodosimetry because no



single assay is sufficiently robust for all potential radiation scenarios, including early-phase acute-exposures, partial-body exposures, and retrospective or prior exposure (eg, biosampling years after exposure). Applications involving triage cytogenetics are also useful for radiological mass casualty events. Various parameters and radiation scenarios are applicable to these assays (Table 6-5). The metaphase-spread dicentric (and ring) chromosome aberration assay is commonly applied in the early

**Figure 6-4.** Schematic for sample accession of peripheral blood lymphocytes for various cytogenetic chromosome aberration assays (premature chromosome condensation assay, metaphase-spread dicentric [and ring] chromosome aberration assay, metaphase-spread fluorescence in situ hybridization translocation assay, and cytokinesis-blocked micronuclei assay) used for radiation dose assessment.

**TABLE 6-5**  
**COMPARISON OF CYTOGENETIC CHROMOSOME ABERRATION ASSAYS**

Cytogenetic Chromosome Aberration Assays	Typical Aberrations Scored for Biodosimetry Applications	Typical Radiation Scenario Applications	Photon Equivalent, Acute Dose Range (Gy) for Whole-Body Dose Assessment	Useful for Partial-Body Exposure Applications?	Useful for Triage Dose Assessment?	Standardization of Assay
Premature chromosome condensation assay	Excess chromosome fragments; dicentric* (and rings); translocations*	Acute (including high doses)	0.2–20	Yes	Yes	NA
Dicentric (and Ring) chromosome aberration assay	Dicentrics (and rings)	Low-level; acute; protracted; prior exposure	0.1–5	Yes	Yes	ISO standard for reference assay (1,000 metaphase spreads or 40 dicentrics); ISO standard for triage assay (20–50 metaphase spreads [pending])
Fluorescent in situ hybridization translocation chromosome aberration (translocation) assay	Dicentric* (and rings); translocations*	Protracted; prior exposure	0.25–4	NA	NA	NA
Cytokinesis block micronucleus assay	Micronuclei	Acute	0.3–5	NA	Yes	ISO standard for reference assay (pending)

ISO: International Organization of Standardization; NA: not applicable

\*Specific chromosome aberrations typically detected by use of centromeric and whole-chromosome specific deoxyribonucleic acid hybridization probes.

Data source: Rojas-Palma C, Liland A, Jerstad AN, et al, eds. *TMT Handbook. Triage, Monitoring and Treatment of People Exposed to Ionizing Radiation Following a Malevolent Act*. Osteras, Hedmark, Norway: Norwegian Radiation Protection Agency; 2009. [http://www.tmt handbook.org/index.php?option=com\\_frontpage&Itemid=1](http://www.tmt handbook.org/index.php?option=com_frontpage&Itemid=1). Accessed March 24, 2011.

phase after radiation exposure. The metaphase-spread fluorescence in situ hybridization translocation assay is typically used in retrospective biodosimetry studies. Variations of the premature chromosome condensation assay are useful for dose assessment at high doses and after partial-body exposures. The cytokinesis-blocked micronuclei assay has been advocated for use in radiological mass casualty events.

Reference laboratories and standards are established

to perform dose assessment by cytogenetics.<sup>50,51</sup> Experts from these laboratories apply the appropriate cytogenetic chromosome aberration assay depending on the specific radiation scenarios encountered and for which they are qualified to perform. Cytogenetic biodosimetry networks, which are composed of expert laboratories from various nations, provide assistance to nations that do not have a reference cytogenetic biodosimetry laboratory or when the needs exceed their capabilities.<sup>50</sup>

**TABLE 6-6**

**ACUTE-PHASE PATIENT ASSESSMENT METHODS: APPLICATION FOR VARIOUS EXPOSURE SCENARIOS**

Assessment Method*	Application for Internal Contamination Assessment	Application for ARS Severity Assessment	Application for Partial-Body Dose Assessment	Applicable for Triage Assessment	Triage Dose (Gy) to Select for Priority Cytogenetic Triage Analysis	ARS Response Category Level to Select for Priority Cytogenetic Triage Analysis <sup>†</sup>	Application for Retrospective Assessment
Direct recording of location history	Yes	NA	Yes	Yes	3-7	NA	Yes
Direct observation of clinical signs and symptoms	NA	Yes	Yes	Yes	3-7	1-4	Yes
Personal monitoring (direct, noninvasive)							
In-vivo EPR	NA	NA	Yes	Yes	3-7	NA	Yes
Portable handheld meters (triage/screening)	Yes	NA	Yes	Yes	NA	NA	NA
Portal monitors (triage/screening)	Yes	NA	NA	Yes	NA	NA	NA
Whole-body counting	Yes	NA	NA	Yes	Yes	NA	Yes
Personal monitoring (indirect, invasive)							
Blood chemistry (amylase activity, C-reactive protein)	No	NA	Yes	Yes	3-7	No	Yes
CBC and differential/lymphocyte count	No	Yes	No	Yes	3-7	1-4	Yes
In-vitro EPR (eg, nails)	No	No	Yes	Yes	3-7	NA	Yes
Nasal swab	Yes	No	Yes	Yes	NA	NA	Yes
Stool sample	Yes	No	No	Yes	NA	NA	Yes
Urine sample (spot; 24 h)	Yes	No	No	Yes	NA	NA	Yes
Cytogenetics (eg, 20-50 metaphase triage; 1,000 metaphase analysis)	NA	Yes	Yes (indirect)	Yes	3-7	NA	Yes
Area monitoring							
Dosimetry results (eg, TLDs, aerial measurements) combined with personal location information	NA	No	No	Yes	3-7	NA	Yes

(Table 6-6 continues)

Table 6-6 continued

ARS: acute radiation syndrome; CBC: complete blood count; EPR: electron paramagnetic resonance; TLD: thermoluminescent dosimeter

\*Personal and area monitoring methods are listed in alphabetical order; their location in the table does not infer priority or preference.

†Response category levels reflect graded severity levels of ARS from mild sublethal (1) to very severe acute lethality (4).

Data sources: (1) Alexander GA, Swartz HM, Amundson SA, et al. BiodosEPR-2006 Meeting: acute dosimetry consensus committee recommendations on biodosimetry applications in events involving uses of radiation by terrorists and radiation accidents. *Radiat Meas.* 2007;42:972–996. (2) Waselenko JK, MacVittie TJ, Blakely WF, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Working Group. *Ann Intern Med.* 2004;140(12):1037–1051

## SUMMARY

Radiation dose or injury assessment is based on multiple biodosimetry-based assays and other physical and biophysical dosimetry approaches. Various dose assessment methodologies are typically used for different radiation scenarios and dose-assessment applications (Table 6-6). The accepted generic multiparameter and early-response approach includes measuring radionuclide contamination and monitoring the exposed individual; observing and recording prodromal signs and symptoms; obtaining complete blood counts with white blood cell differential; sampling blood for the chromosome-aberration cytogenetic bioassay using the “gold standard” dicentric assay (translocation assay for long times after exposure) for dose assessment; bioassay sampling, if appropriate, to determine radioactivity contamination; and using other available dosimetry approaches.

In the event of a radiological mass casualty incident, local, national, and international resources need

to be integrated to provide suitable dose assessment and medical triage and diagnoses.<sup>4</sup> This capability should be broadly based and include (a) training and equipping local responders with tools and knowledge to provide early radiological triage, (b) establishing radiological teams capable of rapidly deploying and providing specialized dose assessment capabilities (ie, radiation screening and radiobioassay sampling, hematology, etc), and (c) access to reach-back expert reference laboratories (eg, cytogenetic biodosimetry, radiation bioassay, EPR dose assessment). This multifaceted capability needs to be integrated into a biodosimetry “concept of operations” for use in a mass casualty radiological emergency.<sup>4</sup> Ongoing research efforts to identify and validate candidate screening and triage assays should ultimately contribute toward approved, regulated biodosimetry devices or diagnostic tests integrated into local, national, and international radioprotection programs.

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## REFERENCES

1. Blakely WF, Salter CA, Prasanna PG. Early-response biological dosimetry—recommended countermeasure enhancements for mass-casualty radiological incidents and terrorism. *Health Phys.* 2005;89(5):494–504.
2. Pellmar TC, Rockwell S; Radiological/Nuclear Threat Countermeasures Working Group. Priority list of research areas for radiological nuclear threat countermeasures. *Radiat Res.* 2005;163(1):115–123.
3. Turteltaub KW, Hartman-Siantar C, Easterly C, Blakely W. *Technology Assessment and Roadmap for the Emergency Radiation Dose Assessment Program*. Washington, DC: US Department of Homeland Security, Radiological and Nuclear Countermeasures Program; 2005. <https://e-reports-ext.llnl.gov/pdf/325832.pdf>. Accessed October 19, 2012.

4. Blakely WF. Early biodosimetry response: recommendations for mass-casualty radiation accidents and terrorism. Paper presented at: Refresher Course for the 12th International Congress of the International Radiation Protection Association; October 19–24, 2008; Buenos Aires, Argentina. [http://www.irpa12.org.ar/PDF/RC/RC\\_12\\_fullpaper.pdf](http://www.irpa12.org.ar/PDF/RC/RC_12_fullpaper.pdf). Accessed March 23, 2011.
5. Fliedner TM, Friesecke I, Beyrer K, eds. *Medical Management of Radiation Accidents: Manual on the Acute Radiation Syndrome*. London, England: British Institute of Radiology; 2001: 1–66.
6. Fliedner TM, Graessle D, Meineke V, Dörr H. Pathophysiological principles underlying the blood cell concentration responses used to assess the severity of effect after accidental whole-body radiation exposure: an essential basis for an evidence-based clinical triage. *Exp Hematol*. 2007;35:8–16.
7. Waselenko JK, MacVittie TJ, Blakely WF, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Working Group. *Ann Intern Med*. 2004;140(12):1037–1051.
8. MacVittie TJ, Farese AM, Jackson W III. Defining the full therapeutic potential of recombinant growth factors in the post radiation-accident environment: the effect of supportive care plus administration of G-CSF. *Health Phys*. 2005;89(5):546–455.
9. Alexander GA, Swartz HM, Amundson SA, et al. BiodosEPR-2006 Meeting: acute dosimetry consensus committee recommendations on biodosimetry applications in events involving uses of radiation by terrorists and radiation accidents. *Radiat Meas*. 2007;42:972–996.
10. Simon SL, Bailiff I, Bouville A, et al. BiodosEPR-2006 consensus committee report on biodosimetric methods to evaluate radiation doses at long times after exposure. *Radiat Meas*. 2007;42:948–971.
11. International Atomic Energy Agency; World Health Organization. *Generic Procedures for Medical Response During a Nuclear or Radiological Emergency*. Vienna, Austria: IAEA; 2005. EPR-MEDICAL 2005.
12. Sine RC, Levine IH, Jackson WE, et al. Biodosimetry Assessment Tool: a postexposure software application for management of radiation accidents. *Mil Med*. 2001;166(12):85–87.
13. Salter CA, Levine IH, Jackson WE, Prasanna PGS, Salomon K, Blakely WF. Biodosimetry tools supporting the recording of medical information during radiation casualty incidents. In: Brodsky A, Johnson RH Jr, Goans RE. *Public Protection from Nuclear, Chemical, and Biological Terrorism: Health Physics Society 2004 Summer School*. Madison, WI: Medical Physics Publishing; 2004: 481–488.
14. Salter CA, Levine IH, Jackson WE, et al. Medical recording tools for biodosimetry in radiation incidents. In: The proceedings of the NATO Human Factors and Medicine Panel Research Task Group 099 Meeting, “Radiation Bioeffects and Countermeasures”; June 21–23, 2005; Bethesda, MD. AFRRI CD 05–2.
15. Waller E, Millage K, Blakely WF, et al. Overview of hazard assessment and emergency planning software of use to RN first responders. *Health Phys*. 2009;97(2):145–156.
16. Armed Forces Radiobiology Research Institute. *AFRRI Pocket Guide: Emergency Radiation Medicine Response*. Bethesda, MD: AFRRI; September 2008. [www.usuhs.mil/afrrri/outreach/pdf/AFRRI-Pocket-Guide.pdf](http://www.usuhs.mil/afrrri/outreach/pdf/AFRRI-Pocket-Guide.pdf). Accessed March 23, 2011.
17. Blakely WF, Ossetrova NI, Manglapus GL, et al. Amylase and blood cell-count hematological radiation-injury biomarkers in a rhesus monkey radiation model—use of multiparameter and integrated biological dosimetry. *Radiat Meas*. 2007;42(6–7):1164–1170.
18. Anno GH, Baum SJ, Withers HR, Young RW. Symptomatology of acute radiation effects in humans after exposure to doses of 0.5–30 Gy. *Health Phys*. 1989;56:821–838.
19. Goans RE, Holloway EC, Berger ME, Ricks RC. Early dose assessment following severe radiation accidents. *Health Phys*. 1997;72(4):513–518.

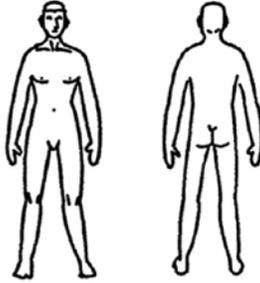
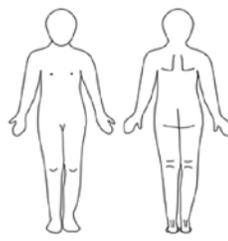
20. Goans RE, Holloway EC, Berger ME, Ricks RC. Early dose assessment in criticality accidents. *Health Phys.* 2001;81(4):46–49.
21. Goans RE. Clinical care of the radiation-accident patient: patient presentation, assessment, and initial diagnosis. In: Ricks RC, Berger ME, O'Hara FM Jr, eds. *The Medical Basis for Radiation-Accident Preparedness: The Clinical Care of Victims. Proceedings of the Fourth International REAC/TS Conference on the Medical Basis for Radiation-Accident Preparedness, March 2001, Orlando, Florida.* Boca Raton, FL: The Parthenon Publishing Group; 2002: 11–22.
22. Fliedner TM. Nuclear terrorism: the role of hematology in coping with its health consequences. *Curr Opin Hematol.* 2006;13(6):436–444.
23. Gus'kova AK, Baranov AE, Gusev IA. Acute radiation sickness: underlying principles and assessment. In: Gusev AE, Gus'kova AK, Mettler FA Jr, eds. *Medical Management of Radiation Accidents.* Boca Raton, FL: CRC Press; 2001: 33–51.
24. Sandgren DJ, Salter CA, Levine IH, Ross JA, Lillis-Hearne PK, Blakely WF. Biodosimetry Assessment Tool (BAT) software-dose prediction algorithm. *Health Phys.* 2010;99(Suppl 5):S171–S183.
25. Graessle DH, Hofer EP, Lehn F, Fliedner TM. Classification of the individual medical severeness of radiation accidents within short time. In: *The 10th Japanese–German Seminar, Nonlinear Problems in Dynamical Systems—Theory and Applications; September 30–October 3, 2002; Hakui, Ishikawa, Japan.*
26. Zhang A, Azizova TV, Wald N, Day R. Changes of ratio of peripheral neutrophils and lymphocytes after radiation exposure may serve as a prognostic indicator of accident severity. In: *Final Program, 49th Annual Meeting of the Health Physics Society, July 11–15, 2004, Washington, DC.* McLean, VA: Health Physics Society; 2004. Abstract. <http://hps.org/documents/49finalprogram.pdf>. Accessed February 1, 2012.
27. Bertho JM, Roy L, Souidi M, et al. New biological indicators to evaluate and monitor radiation-induced damage: an accident case report. *Radiat Res.* 2008;169:543–550.
28. Bertho JM, Roy L. A rapid multiparametric method for victim triage in cases of accidental protracted irradiation or delayed analysis. *Br J Radiol.* 2009;82:764–770.
29. Blakely WF, Ossetrova NI, Manglapus GL, et al. Amylase and blood cell-count hematological radiation-injury biomarkers in a rhesus monkey radiation model—use of multiparameter and integrated biological dosimetry. *Radiat Meas.* 2007;42(6–7):1164–1170.
30. Blakely WF, Ossetrova NI, Whitnall MH, et al. Multiple parameter radiation injury assessment using a nonhuman primate radiation model—biodosimetry applications. *Health Phys.* 2010;98:153–159.
31. International Commission on Radiation Units and Measurements. *Retrospective Assessment of Exposures to Ionizing Radiation (Report 68).* Bethesda, MD: ICRU; 2002.
32. International Atomic Energy Association. *Use of Electron Paramagnetic Resonance Dosimetry With Tooth Enamel for Retrospective Dose Assessment TECDOC-1331.* Vienna, Austria: IAEA; 2002.
33. Prasanna PG, Blakely WF, Bertho JM, et al. Synopsis of partial-body radiation diagnostic biomarkers and medical management of radiation injury workshop. *Radiat Res.* 2010;173(2):245–253.
34. Bertho JM, Demarquay C, Frick J, et al. Level of Flt3-ligand in plasma: a possible new bio-indicator for radiation-induced aplasia. *Int J Radiat Biol.* 2001;77(6):703–712.
35. Blakely WF, Miller AC, Grace MB, et al. Radiation biodosimetry: applications for spaceflight. *Adv Space Res.* 2003;31(6):1487–1493.
36. Blakely WF, Miller AC, Grace MB, McLeland CB, Muderhwa JM, Prasanna PGS. Dose assessment based on molecular biomarkers. In: *Radiation Safety Aspects of Homeland Security and Emergency Response, Proceedings of the 36th Midyear Topical Meeting; 2003.* McLean, VA: Health Physics Society; 229–234. Abstract. <http://hps.org/meetings/midyear/abstract434.html>. Accessed February 1, 2012.

37. Becciolini A, Giannardi G, Cionini L, Porciani S, Fallai C, Pirtoli L. Plasma amylase activity as a biochemical indicator of radiation injury to salivary glands. *Acta Radiol Oncol.* 1984;23:9–14.
38. Leslie MD, Dische S. Changes in serum and salivary amylase during radiotherapy for head and neck cancer: a comparison of conventional fractionated radiotherapy with CHART. *Radiother Oncol.* 1992;24(1):27–31.
39. Hofmann R, Schreiber GA, Willich N, Westhaus R, Bögi KW. Increased serum amylase in patients as a probable bioindicator for radiation exposure. *Strahlenther Onkol.* 1990;166(10):688–695.
40. Becciolini A, Porciani S, Lanini A, Balzi M, Faroani P. Proposal for biochemical dosimeter for prolonged space flights. *Phys Med.* 2001;17(Suppl 1):185–186.
41. Akashi M, Hirama T, Tanosaki S, et al. Initial symptoms of acute radiation syndrome in the JCO criticality accident in Tokai-mura. *J Radiat Res (Tokyo).* 2001;42(Suppl):S157–S166.
42. Kashima HK, Kirkham WR, Andrews JR. Post-irradiation sialadenitis: a study of clinical features, histopathologic changes and serum enzyme variations following irradiation of human salivary glands. *AJR Am J Roentgenol.* 1965;94:271–291.
43. Becciolini A, Porciani S, Lanini A, Benucci A, Castagnoli A, Pupi A. Serum amylase and tissue polypeptide antigen as biochemical indicators of salivary gland injury during iodine-131 therapy. *Eur J Nucl Med.* 1994;21(10):1121–1125.
44. Chen IW, Kereiakes JG, Silberstein EB, Aron BS, Saenger EL. Radiation-induced change in serum and urinary amylase levels in man. *Radiat Res.* 1973;54:141–151.
45. Becciolini A, Porciani S, Lanini A. Marker determination for response monitoring: radiotherapy and disappearance curves. *Int J Biol Markers.* 1994;9(1):38–42.
46. Hennequin C, Cosset JM, Cailleux PE, et al. Blood amylase: a biological marker in irradiation accidents? Preliminary results obtained at the Gustave-Roussy Institut (GRI) and a literature review [in French]. *Bull Cancer.* 1989;76(6):617–624.
47. Dubray B, Girinski T, Thames HD, et al. Post-irradiation hyperamylasemia as a biological dosimetry. *Radiother Oncol.* 1992;24(1):21–26.
48. Dainiak N. Hematologic consequences of exposure to ionizing radiation. *Exp Hematol.* 2002;30:513–528.
49. Koenig KL, Goans RE, Hatchett RJ, et al. Medical treatment of radiological casualties: current concepts. *Ann Emerg Med.* 2005;45(6):643–652.
50. Voisin P, Barquinero F, Blakely B, et al. Towards a standardization of biological dosimetry by cytogenetics. *Cell Mol Biol.* 2002;48(5):501–504.
51. Blakely WF, Carr Z, Chu MC, et al. WHO 1st consultation on the development of a global biodosimetry laboratories network for radiation emergencies (BioDoseNet). *Radiat Res.* 2009;171(1):127–139.

**ATTACHMENT 1: ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE  
ADULT/PEDIATRIC FIELD MEDICAL RECORD**

**AFRRI Adult/Pediatric Field Medical Record**

Adapted from DD Form 1380, U.S. Field Medical Card

1. Name (last, first)		Rank/Grade		<input type="checkbox"/> Male	<input type="checkbox"/> Female
SSN		Specialty code		Religion	
2. Unit		Force		Nationality	
<input type="checkbox"/> A <input type="checkbox"/> AF <input type="checkbox"/> N <input type="checkbox"/> MC <input type="checkbox"/> Civilian <input type="checkbox"/> BC <input type="checkbox"/> NBI		<input type="checkbox"/> Disease		<input type="checkbox"/> Psych	
3. Injury		Adult Front                      Back 		Child Front                      Back 	
				<input type="checkbox"/> Airway <input type="checkbox"/> Head <input type="checkbox"/> Wound <input type="checkbox"/> Neck/back injury <input type="checkbox"/> Burn <input type="checkbox"/> Amputation <input type="checkbox"/> Stress <input type="checkbox"/> Other (specify)	
4. Level of consciousness					
<input type="checkbox"/> Alert		<input type="checkbox"/> Pain response			
<input type="checkbox"/> Verbal response		<input type="checkbox"/> Unresponsive			
5. Pulse		Time		6. Tourniquet <input type="checkbox"/> No <input type="checkbox"/> Yes	
7. Morphine <input type="checkbox"/> No <input type="checkbox"/> Yes		Dose		8. IV	
		Time		Time	
9. Treatment/observations/current medication/allergies/NBC (antidote)					
10. Disposition		<input type="checkbox"/> Returned to duty <input type="checkbox"/> Evacuated <input type="checkbox"/> Deceased		Time	
11. Provider/unit				Date (YYMMDD)	
12. Reassessment					
Date (YYMMDD)			Time of arrival		
Time					
BP					
Pulse					
Resp					
Date/time		13. Clinical comments/diagnosis			
		14. Orders/antibiotics (specify)/tetanus/IV fluids			
15. Provider				Date (YYMMDD)	
16. Disposition		<input type="checkbox"/> Returned to duty <input type="checkbox"/> Evacuated <input type="checkbox"/> Deceased		Time	
17. Religious services		<input type="checkbox"/> Baptism <input type="checkbox"/> Anointing <input type="checkbox"/> Confession		<input type="checkbox"/> Prayer <input type="checkbox"/> Communion <input type="checkbox"/> Other Chaplain	

**ATTACHMENT 2: ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE  
BIODOSIMETRY WORKSHEET**

**Armed Forces Radiobiology Research Institute  
Biodosimetry Worksheet**

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

**Reporting Authority** (person(s) creating this page of the report)

Last name: \_\_\_\_\_ First name: \_\_\_\_\_ Country of origin: \_\_\_\_\_  
 Unit: \_\_\_\_\_ Phone: \_\_\_\_\_ Fax: \_\_\_\_\_ Email: \_\_\_\_\_  
 Location: \_\_\_\_\_ Date (yymmdd): \_\_\_\_\_ Time: \_\_\_\_\_

**Casualty**

Last name: \_\_\_\_\_ First name: \_\_\_\_\_ Rank: \_\_\_\_\_  
 Country of origin: \_\_\_\_\_ Parent unit: \_\_\_\_\_ Parent unit location: \_\_\_\_\_  
 Parent unit phone: \_\_\_\_\_ Unit e-mail: \_\_\_\_\_ Unit fax: \_\_\_\_\_ Casualty location: \_\_\_\_\_

History of presenting injury  
(conventional and/or radiation): \_\_\_\_\_

History of previous  
radiation exposure: \_\_\_\_\_

Past medical  
history (general): \_\_\_\_\_

Medical countermeasures  
(e.g., antiemetics, transfusion), specify: \_\_\_\_\_

Administered (where, when, route): \_\_\_\_\_

**Exposure conditions**

Date of exposure (yymmdd): \_\_\_\_\_ Exposure location: \_\_\_\_\_ Time of exposure: \_\_\_\_\_  
 Weather conditions (at time of exposure): \_\_\_\_\_

**Exposure results**  
Describe incident: \_\_\_\_\_

**External exposure overview**  
 Body exposure:  Total  Partial  Uncertain  
 Shielding confounder:  Yes  No

**Contamination overview**  
 External contamination:  Yes  No  
 Internal contamination:  Yes  No  
 Contaminated wound:  Yes  No

If wound(s)  
are radiation  
contaminated,  
please provide  
details here: \_\_\_\_\_

<b>Biodosimetric assays overview</b>	Sampling date, time yymmdd (time)	Estimated time post-exposure (h)	Dose (Gy)	Reference radiation quality and dose rate (Gy/min)
Time onset of vomiting:	_____	_____	_____	_____
Lymphocyte counts or depletion kinetics:	_____	_____	_____	_____
Urine bioassay:	_____	_____	_____	_____
Cytogenetic biodosimetry:	_____	_____	_____	_____
Other:	_____	_____	_____	_____

**ARS response category overview** (maximum grading 0-4; see pages 4 through 6 for guidance)

N: \_\_\_\_\_ C: \_\_\_\_\_ G: \_\_\_\_\_ H: \_\_\_\_\_ = RC: \_\_\_\_\_ days after radiation exposure: \_\_\_\_\_

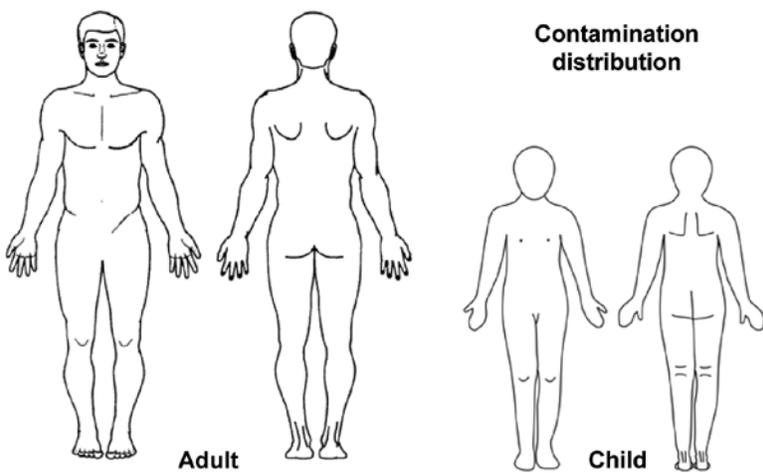
**Contamination: Dose Assessment** (person(s) creating this page of the report)

Last name: \_\_\_\_\_ First name: \_\_\_\_\_ Unit: \_\_\_\_\_  
 Phone: \_\_\_\_\_ Fax: \_\_\_\_\_ E-mail: \_\_\_\_\_ Country: \_\_\_\_\_  
 Date dose assessed (yymmdd): \_\_\_\_\_ Time dose assessed: \_\_\_\_\_ Place: \_\_\_\_\_

**Contamination: external/internal**

Substance trademark (if applicable): \_\_\_\_\_ Solid:  Yes  No  
 Particulate (P):  Yes  No Gaseous (G):  Yes  No  
 Liquid (L):  Yes  No Aerosol (L/G):  Yes  No  
 Radionuclide(s): \_\_\_\_\_ Aerosol (P/G):  Yes  No  
 Activity (Bq): \_\_\_\_\_ Chemical compound(s): \_\_\_\_\_

Comments:



**Route of intake** (in case of internal contamination)

Inhalation:  Yes  No Ingestion:  Yes  No Other:  Yes  No  
 Cutaneous:  Yes  No Injection:  Yes  No If yes, specify: \_\_\_\_\_

**Contamination assessment**

Contamination measurement: \_\_\_\_\_ Detection device: \_\_\_\_\_  
 Counts per minute: \_\_\_\_\_ Estimated activity: \_\_\_\_\_  
 Decontamination measures: \_\_\_\_\_ Residual contamination: \_\_\_\_\_  
 Measures taken to prevent uptake: \_\_\_\_\_  
 Measures taken to increase excretion: \_\_\_\_\_  
 Measures taken to minimize re-absorption: \_\_\_\_\_

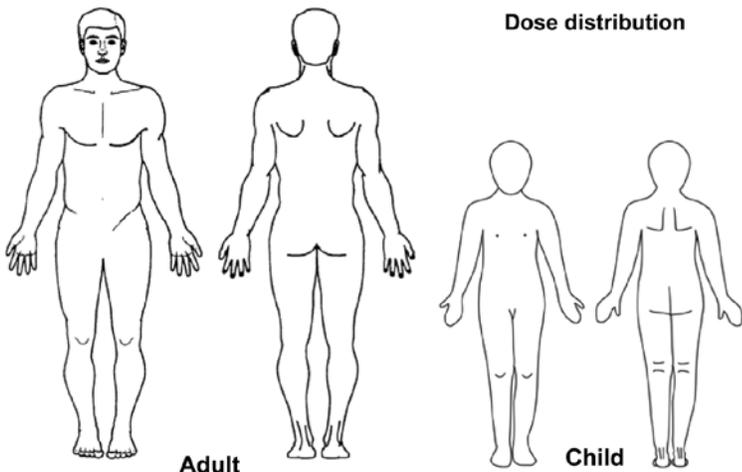
**External Exposure: Dose Assessment** (person(s) creating this page of the report)

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 ( $\alpha$ ):  Yes  No      Beta ( $\beta$ ):  Yes  No      Neutron (n):  Yes  No  
 Gamma ( $\gamma$ ):  Yes  No      X-ray (x):  Yes  No      Mixed (n/ $\gamma$ ):  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): \_\_\_\_\_



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:	_____	_____	_____	_____

**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 (yyymmdd): \_\_\_\_\_  
 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)

	C	D	C	D	C	D	C	D	C	D	C	D
Lymphocytes ( $\times 10^9$ )/liter:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Granulocytes ( $\times 10^9$ )/liter:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Neutrophils ( $\times 10^9$ )/liter:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Platelets ( $\times 10^9$ )/liter:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Blood loss:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Infection:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Maximum grading H:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Response category (RC) =	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Days after exposure:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____

**ARS Responses Assessment** (continued from page 4)

Date format: yymmdd (time)	Onset (date/time)	Duration (hours)	Comments:
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:	_____	_____	

Adapted from:

- 1.NATO Standardization Agreement (STANAG 2474). Determination and Recording of Ionizing Radiation Exposure for Medical Purposes. Appendix 1, 2003.
- 2.Fliedner TM, Friesoecke 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 -679.
- 4.Radiation Event Medical Management (REMM). Guidance on Diagnosis & Treatment for Health Care Providers. Accessed 24 Oct 2007, from <http://www.remm.nlm.gov/ars.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.

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

<b>Symptom</b>	<b>Degree 1</b>	<b>Degree 2</b>	<b>Degree 3</b>	<b>Degree 4</b>
<b>Neurovascular system</b>				
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
<b>Cutaneous system</b>				
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 intermittent 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
<b>Gastrointestinal system</b>				
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
<b>Hematopoietic system</b>				
Lymphocyte changes: (reference value, 1.4–3.5 × 10 <sup>9</sup> 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 <sup>9</sup> 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 <sup>9</sup> 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

