Review

BiodosEPR-2006 Meeting: Acute dosimetry consensus committee recommendations on biodosimetry applications in events involving uses of radiation by terrorists and radiation accidents

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Abstract

In the aftermath of a radiological terrorism incident or mass-casualty radiation accident, first responders and receivers require prior guidance and pre-positioned resources for assessment, triage and medical management of affected individuals [NCRP, 2005. Key elements of preparing emergency responders for nuclear and radiological terrorism. NCRP Commentary No. 19, Bethesda, Maryland, USA]. Several recent articles [Dainiak, N., Waselenko, J.K., Armitage, J.O., MacVittie, T.J., Farese, A.M., 2003. The hematologist and radiation casualties. Hematology (Am. Soc. Hematol. Educ. Program) 473–496; Waselenko, J.K., MacVittie, T.J., Blakely, W.F., Pesik, N., Wiley, A.L., Dickerson, W.E., Tsu, H., Confer, D.L., Coleman, C.N., Seed, T., Lowry, P., Armitage, J.O., Dainiak, N., Strategic National Stockpile Radiation Working Group, 2004. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann. Intern. Med. 140(12), 1037–1051; Blakely, W.F., Salter, C.A., Prasanna, P.G., 2005. Early-response biological dosimetry—recommended countermeasure enhancements for mass-casualty radiological incidents and terrorism. Health Phys. 89(5), 494–504; Goans, R.E., Waselenko, J.K., 2005. Medical management of radiation casualties. Health Phys. 89(5), 505–512; Swartz, H.M., Iwasaki, A., Walczak, T., Demidenko, E., Salikhov, I., Lesniewski, P., Starewicz, P., Schauer, D., Romanyukha, A., 2005. Measurements of clinically significant doses of ionizing radiation using non-invasive in vivo EPR spectroscopy of teeth in situ. Appl. Radiat. Isot. 62, 293–299;

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Weisdorf, D., Chao, N., Waselenko, J.K., Dainiak, N., Armitage, J.O., McNiece, I., Confer, D., 2006. Acute radiation injury: contingency planning for triage, supportive care, and transplantation. Biol. Blood Marrow Transplant. 12(6), 672–682], national [National Council of Radiation Protection and Measurements (NCRP), 1994. Management of persons accidentally contaminated with radionuclides. NCRP Report No. 65, Bethesda, Maryland, USA; NCRP, 2001. Management of terrorist events involving radioactive material. NCRP Report No. 138, Bethesda, Maryland, USA; NCRP, 2005. Key elements of preparing emergency responders for nuclear and radiological terrorism. NCRP Commentary No. 19, Bethesda, Maryland, USA] and international [IAEA, 2005. Generic procedures for medical response during a nuclear or radiological emergency. EPR-Medical 2005, IAEA, Vienna, Austria] agencies have reviewed strategies for acute-phase biodosimetry. Consensus biodosimetric guidelines include: (a) clinical signs and symptoms, including peripheral blood counts, time to onset of nausea and vomiting and presence of impaired cognition and neurological deficits, (b) radioactivity assessment, (c) personal and area dosimetry, (d) cytogenetics, (e) in vivo electron paramagnetic resonance (EPR) and (f) other dosimetry approaches (i.e. blood protein assays, etc.). Emerging biodosimetric technologies may further refine triage and dose assessment strategies. However, guidance is needed regarding which biodosimetry techniques are most useful for different radiological scenarios and consensus protocols must be developed.

The Local Organizing Committee for the Second International Conference on Biodosimetry and Seventh International Symposium on EPR Dosimetry and Applications (BiodosEPR-2006 Meeting) convened an Acute Dosimetry Consensus Committee composed of national and international experts to: (a) review the current literature for biodosimetry applications for acute-phase applications in radiological emergencies, (b) describe the strengths and weaknesses of each technique, (c) provide recommendations for the use of biodosimetry assays for selected defined radiation scenarios, and (d) develop protocols to apply these recommended biological dosimetry techniques with currently available supplies and equipment for first responders.

The Acute Dosimetry Consensus Committee developed recommendations for use of a prioritized multiple-assay biodosimetric-based strategy, concluding that no single assay is sufficiently robust to address all of the potential radiation scenarios including management of mass casualties and diagnosis for early medical treatment. These recommendations may be used by first responders/first receivers that span time-windows of (i.e. 0–5 days) after the radiological incident for three radiological scenarios including: (a) radiation exposure device (RED), (b) radiological dispersal device (RDD), and (c) an improvised (or otherwise acquired) nuclear device (IND). Consensus protocols for various bioassays (i.e. signs and symptoms recording, bioassay sampling for radioactivity analysis, nail-clipping sampling for EPR analysis and blood collection for hematology, cytogenetics, and blood chemistry analyses) are presented as Appendix materials. As stated in NCRP Commentary No. 19 [NCRP, 2005. Key elements of preparing emergency responders for nuclear and radiological terrorism. NCRP Commentary No. 19, Bethesda, Maryland, USA], multi-parameter triage (i.e. time to vomiting, lymphocyte kinetics, and other biodosimetry indicators) offers the current best strategy for early assessment of absorbed dose.

Contents

1. Introduction and requirements for acute dosimetry

This article focuses on the current status of techniques for estimating absorbed doses in the aftermath of incidents that potentially expose humans to ionizing radiation. The high potential for the occurrence of these incidents result in the need to provide planners, decision makers, first responders and receivers (i.e. physicians and nurses) with guidance to perform triage based on dose assessment, so that those who are at risk of significant acute radiation effects are identified and entered into the health care system. Individuals without combined injury and sub clinical exposures (i.e. less than 1.5 Gy) can be followed as outpatients. Combined injury patients in this context are defined as individuals exposed to radiation and trauma, infectious diseases, or chemical agents. Individuals with significant absorbed doses (i.e. > 1.5–10 Gy) can be referred to hospitals for treatment, while those with higher absorbed doses (i.e. > 10 Gy) and those with significant radiation-induced damage to both the bone marrow and damage to other organs resulting from mechanical trauma and/or burns may be triaged for compassionate care or to heroic (and resource intensive) measures, if resources are available. Dose assessments contribute but should not be used alone to dictate life-saving medical treatment decisions, since confounding factors such as dose rate and radiation quality can profoundly influence the clinical outcome of individual exposed to ionizing radiation (Fliedner et al., 2001; Salter et al., 2004; Waselenko et al., 2004).

Effective triage requires the availability of methods to assess absorbed dose rapidly in the field. It is also important to identify individuals who have minimal or no exposure, so they can be reassured, and do not enter the potentially over burdened health care system. The need for adequate and rapid dosimetry is likely to increase in the near future because of the considerable amount of innovative effort that is being devoted to the development of new medical management approaches (Gorin et al., 2006), mitigating agents, and treatments (Sémont et al., 2006), especially through the efforts of the Centers for Medical Countermeasures against Radiation (CMCRs) supported by the U.S. National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID). Some of these agents are likely to be effective but will need to be administered very early to have maximum efficacy. However, since some of these therapies may have significant potential risk for toxicity, they should be administered only to individuals who have significant exposures.

There are a number of promising techniques that are expected to provide accurate estimates of absorbed dose under the conditions that are likely to be present with an act of radiological terrorism or a large-scale accident, especially if used in a complementary manner. The focus of this article is to provide an overview of the most promising approaches, to indicate their potential strengths and weaknesses, and to predict the likely near-term developments. These approaches include some methods that already are in active use but that are not optimized for the needs of a large-scale incident. The appendices include draft protocols for the use of current and developing methods.

There are detailed procedures in place that provide guidance for initial and subsequent responses based on clinical signs and symptoms and existing hematologically based technologies (Dainiak, 2002; Dainiak et al., 2003, 2006; Salter et al., 2004; Blakely et al., 2005). Potentially effective mitigating approaches are available that appear to have acceptable toxicities, especially if utilized under close medical supervision. These mitigating approaches have been integrated into guidance documents prepared by the Center for Disease Control and Prevention's Strategic National Stockpile Radiation Working Group (Waselenko et al., 2004). Nearly identical mitigation strategies have been subsequently developed by a European Working Group (Gorin et al., 2006). The appendices to this article provide a summary of the recommendations, which currently are the best available guidance based on procedures that can be implemented today.

2. Current status of biodosimetry methods for radiation incidents and accidents

2.1. Cytogenetics

Cytogenetic biodosimetry (CB) is a widely accepted method for dose assessment following acute irradiation of bone marrow and internal organs. CB provides individual dose assessment based on the measurement of radiation-induced effects in the human body. This permits triaging of individuals with higher doses requiring more medical resources from those needing fewer resources. However, CB has significant limitations. Typically a CB-based dose assessment requires about 4–5 days, including timely transport, to process and read the sample, and most laboratories will be able to process up to 50–200 samples per day at a maximum. Research on CB for more efficient field capability is desirable to increase capacity in order to provide

Table 1
Comparison of various parameters for cytogenetic biodosimetry for absorbed dose assessment

Assay	Useful dose range (Gy)[a]	Relative cost[a]	Time required[a]	Partial-body applications	Automation	Retrospective dose applications
DA	0.2 ⩾ 5	$$	High	Yes	Medium	No
FISH	0.25 ⩾ 3	$$$	High	No	Low	Yes
CBMA	0.3–5	$	Low	No	High	No
PCC	0.2–10	$$	Medium	Yes	Medium	No

[a]Varies with number scored.

optimal management of possible mass-casualty scenarios. The micronuclei assay can be performed in less time (i.e. 1–2 days, excluding transport time), however, with lower sensitivity and specificity.

The currently available techniques for assessment of absorbed dose have been reviewed (IAEA, 2001). Table 1 provides a comparison of selected parameters for application of these internationally accepted cytogenetic-based biodosimetry techniques. The lymphocyte metaphase-spread dicentric assay (DA) represents the most robust cytogenetic bioassay for early-response dose assessment. For example, the DA is unique among the cytogenetic bioassays since it can provide information on whole-body (homogeneous) vs. partial-body (heterogeneous) exposures (IAEA, 1986). Some new adaptations of cytogenetic techniques use skin cells as biological material. These techniques are under development (Pouget et al., 2004).

2.1.1. Dicentric assay

Dose assessment based on the DA has been a component of accidental radiation dose assessment for decades (IAEA, 1986). In this assay, activated lymphocytes are arrested in metaphase and fixed slide preparations are analyzed for the presence of dicentric and ring chromosomes. The metaphase spreads are then analyzed for the presence of dicentric and ring chromosomes. Based on calibration curves produced from in vitro exposures, a dose estimate can be made according to the number of dicentrics and rings detected per cell. This assay is generally accepted as the most specific and sensitive currently available method for determining doses from recent (i.e. within days to ∼ 6 months) exposures to ionizing radiation (Bender et al., 1988; Voisin et al., 2002). In 2004, the International Organization for Standardization (ISO) accepted DA as an international standard and a published guideline (ISO, 2004) for service laboratories performing radiation biological dosimetry using cytogenetics. Experience with DA in the evaluation of hundreds of cases of suspected or verified radiation overexposures throughout the world has demonstrated the usefulness and limitations of this technique for the purpose of providing personal absorbed dose estimates in the absence of physical dosimetry. For instance, this assay is useful for acute, recent exposures and can determine if the exposure was homogeneous (based on the intensity of the changes in individual cells). However, the usefulness of DA is greatly reduced for measuring previous exposures (> 6 months) due to the half-life of cells containing dicentric and ring aberrations.

In the case of a large-scale nuclear or radiological incident, it is necessary to quickly identify exposed individuals for the purposes of medical intervention and to identify first responders who may need to limit their total absorbed dose. In its current state DA is not suitable for this purpose. Therefore, considerable efforts are underway to improve the DA to overcome current limitations on the number of samples that can be measured and the time required to measure them. For rapid triage biological dosimetry, only 50 metaphase spreads need to be scored for each sample. Scoring of a smaller number of cells results in a higher absorbed dose threshold (i.e. 1 Gy) which is considered sufficient for identification of individuals who will require medical treatment for their exposures (Lloyd et al., 2000). An additional strategy for increasing throughput is to develop an interactive network between experienced laboratories that could act as reference laboratories, along with the assistance of clinical cytogenetics laboratories as satellite scoring laboratories. By maintaining the scoring capabilities in the satellite laboratories through a series of training exercises and intercomparisons, the capacity for the dicentric analysis could be greatly increased (Miller et al., 2007). Some level of automation is also possible for this assay. Metaphase finders decrease the time spent finding the metaphase spreads on the slide. Attempts to automate the scoring of the chromosome aberrations have had mixed results. Automation of the sample preparation is being investigated and would be useful in a casualty situation involving large numbers of victims (Prassanna et al., 2004, 2005). However, automation remains expensive and actually limited to few laboratories. Some work has also been done on adapting this method to the flow cytometer. By fluorescently labeling both the chromosomes and centromeres in a single chromosome suspension, it should be possible to detect dicentric chromosomes as those having two centromeric signals. However, this method has been limited to date by the sensitivity of existing flow cytometers. As long as the method requires that the cells be cultured and go through one mitosis, it will not be feasible to apply this very valuable technique for immediate triage in the field.

2.1.2. Fluorescence in situ hybridization (FISH) assay

A disadvantage of DA is that the damage is unstable and is eliminated from the peripheral blood lymphocytes as the lymphocyte pool repopulates. More persistent, stable translocations caused by radiation can be measured using FISH (Pinkel et al., 1986). In this method, any number of chromosomes can be labeled with chromosome-specific fluorescently labeled

DNA probes allowing exchanges between chromosomes to be identified using fluorescent microscopy. The stability of these translocations is thought to remain high over decades, however, the applicability of this approach is still under investigation (Roy et al., 2006). Another limitation of this assay is that the background number of translocations can vary between individuals due to differences in a variety of lifestyle factors and age. Without a pre-exposure sample, accurate dosimetry is difficult to achieve, especially for lower doses.

The FISH method can be extended to include up to 23 different fluorescent markers (spectral karyotyping or MFISH) to label all human chromosomes. This feature permits the detection of much more damage with these techniques, which could be useful for understanding the underlying mechanisms of the exposure (Szeles et al., 2006). Many research laboratories use the FISH method for CB measurements, however, the cost and time of analysis using this current state of development limits its practical use at this time for dose assessment in mass-casualty situations.

2.1.3. Cytokinesis block micronucleus (CBMN) assay

CBMN assay is an alternative for the DA. Micronuclei are formed during cell division when a whole chromosome or an acentric chromosome fragment does not integrate into the nucleus of the daughter cell. When cytokinesis is inhibited, binucleated cells result after the first mitotic division and these binucleated cells can be scored for the presence of micronuclei (Fenech and Morley, 1985, 1986). This assay requires less time and fewer skilled technical staff than DA, due to the simple shape of the micronuclei (Leonard et al., 2005). Automated image analysis of the binucleated cells (Varga et al., 2004) is possible and progress has been made in adapting this assay to the flow cytometer (Avlasevich et al., 2006). One disadvantage of this assay, like the FISH assay, is the variability in the background level of micronuclei based on age and lifestyle factors (Fenech et al., 1999). This limits the lower detection level to about $\geqslant 0.3$ Gy (Thierens et al., 1991). This would not be limiting for the use of this assay for emergency medical triage in radiological mass-casualty situations.

2.1.4. Premature chromosome condensation (PCC) assay

One limitation of assays requiring lymphocyte stimulation is that cells receiving higher absorbed doses also experience a delay in cell-cycle progression and may never reach mitosis. This can result in a large underestimation when evaluating absorbed doses > 5 Gy. Chromosomes, however, can be forced to condense prematurely by fusing human lymphocytes with Chinese hamster ovary (CHO) mitotic cells in the presence of polyethylene glycol (PEG) (Johnson and Rao, 1970). This allows measurement of chromosomal aberrations without the requirement for damaged cells to reach mitosis enabling dose estimates to be acquired even after life-threatening exposures to radiation. Also, since this assay can better measure the proportion of exposed cells it is very useful in detecting partial-body exposures and particularly small localized exposures (Darroudi et al., 1998; Blakely et al., 1995). Recently, chemical induction

of PCC assay has been developed using inhibitors of protein phosphatase (i.e. okadaic acid and calyculin A), however, this method for PCC must be used in conjunction with lymphocyte stimulation (Kanda et al., 1999; Prasanna et al., 2000; Durante et al., 1998).

2.2. Electron paramagnetic resonance (EPR, ESR)

Exposure of humans to ionizing radiation results in radiation-induced changes that can be measured and, depending on the absorbed dose, quantified. The use of EPR for biodosimetry is based on the capability of the technique to specifically and sensitively measure unpaired electron species which are created in proportion to the absorbed dose to humans exposed to ionizing radiation. While the lifetimes of these species are very short (i.e. nanoseconds) in aqueous systems such as most biological tissues, the radiation-induced signals can be extremely stable in non-aqueous media, including teeth, bone, fingernails, and hair. The potential for using EPR to measure absorbed doses was first recognized and reported by Brady et al. (1968). EPR was subsequently used for in vitro retrospective analyses of exfoliated teeth for measuring absorbed doses in populations from Japan and the Former Soviet Union.

EPR is a magnetic resonance technique that can be carried out at any frequency (v) or magnetic field (H) such that the resonance conditions are met: $hv = g\beta H$ (β is the magnetic moment of the electron, g is a spectroscopic constant). The usual frequency used in the laboratory is 9500 MHz (i.e. X-band) and the corresponding magnetic field is 330 mT. Use of X-band EPR yields high sensitivity but it cannot be used in the presence of large amounts of water. Therefore, it is suitable only for in vitro measurements with relatively dry samples (e.g. isolated teeth).

In view of the limitations of obtaining isolated teeth under mass-casualty conditions, it is essential to be able to make the measurements in vivo. Attempts have been made to develop such capabilities using 9500 MHz (Ikeya and Ishii, 1989; Yamanaka et al., 1993). With the development of modern sensitive in vivo spectrometers operating at 1200 MHz accurate in vivo measurements have been made in research animals (Miyake et al., 2000) and subsequently in human subjects using low-frequency EPR (1200 MHz) (Swartz et al., 2005, 2006). The safety and effectiveness of this approach have been demonstrated with a fixed-magnet system. The attractiveness of this approach is enhanced by the fact that the readout is immediate and, therefore, avoids the problems involved with the use of remote laboratories. At the present time this appears to be the only biodosimetric technique with this capability.

Currently three approaches using EPR have potential value in estimating absorbed dose under emergency conditions: in vivo measurements of teeth, in vitro measurements of small pieces of teeth or tooth biopsies, and in vitro measurements of fingernail or toenail clippings. It is predicted that within 1–2 years these techniques will be more widely available. The characteristics of these approaches are similar, except as noted in the discussion of the individual approaches. With fast measurements

(i.e. < 5 min) the methods can provide rapid estimates of clinically significant absorbed doses. More precise estimates of absorbed dose, which may be especially useful for helping to define therapy, can be made by extending the data acquisition period.

Each of these EPR-based techniques are non-invasive or minimally invasive (i.e. for the fingernails one must clip the fingernail as is done in routine trimming in adults) and they provide immediate readout at any time after the exposure, even when using minimally trained personnel. Measurements of radiation-induced changes in teeth can be made at any time interval up to hundreds or thousands of years post exposure. Measurements in fingernails can be made up to 30 days after the event or even longer if the samples are collected within a few hours after the event and stored at low temperature.

2.2.1. In vivo EPR measurements of teeth

In vivo measurements of radiation-induced EPR signals in teeth currently utilize a large permanent magnet (40 mT) and, in principle, this system could be deployed in the field using a small vehicle. While clones of this system would be an effective component of large deployment teams, a smaller magnet system would facilitate wider distribution of this capability. The feasibility of such magnet systems has been demonstrated (see Swartz et al., 2007). These are in a form that could be incorporated into a helmet-like structure that would fit over the head. An intraoral magnet is also being developed. It is anticipated that within several years, the technology will be advanced to a point where it may be possible to obtain sufficient sensitivity with lower frequencies and thus lower the requirements for the magnetic field. This would further decrease the size of the magnet that is needed.

The current laboratory-based system can make measurements comfortably in human subjects with a 5-min acquisition time providing dose resolution of ±0.75 Gy (1 SD) and a threshold of not more than 2.0 Gy, with the result being immediately available. There are a number of areas in which improvements should be feasible within 1–2 years. Improvements that are in process include: increasing the sensitivity of the existing types of resonators and the number of teeth in which the measurement is made by changing the size and/or shape of the resonator, improving data analysis, increasing microwave power, and reducing sources of noise. Dose resolution can be improved immediately by extending the time for the measurement, with the increase being proportional to the square root of the time of the measurements (i.e. increasing acquisition time from 5 to 20 min would increase the resolution by a factor of two) and by making the measurements in more than one tooth simultaneously.

While the threshold, sensitivity, and accuracy can be improved further, there are some caveats that pertain to this method regardless of such improvements. The measured quantity is absorbed dose to teeth, not the critical organs of interest in radiation protection. This is not a problem if the exposure is homogeneous. In the event of an asymmetric exposure it may be feasible to utilize the Monte Carlo simulations of doses to human teeth from photon sources of eight standard irradiation

geometries that have been performed and a set of dose conversion coefficients (DCCs) were calculated for 30 different tooth cells (Ulanovsky et al., 2005). DCCs were determined as ratios of tooth absorbed dose to air kerma for monoenergetic photon sources. To facilitate handling of the data set a software utility has been developed. The utility plots the DCC and computes conversion factors from enamel dose to air kerma and from enamel dose to organ dose for user-supplied discrete and continuous photon spectra.

The utility of EPR measurements for decision-making will depend on the homogeneity of the exposure and the type of radiation. The latter is noted because neutrons contribute very little to the EPR signal in teeth due to the low amount of hydrogen atoms in the enamel (Zdravkova et al., 2003; Trompier et al., 2004). If the dose has a major contribution from ingested or inhaled radionuclides, the dose delivered to the teeth may not closely reflect the dose to critical tissues.

2.2.2. Measurements in fingernails (or toenails)

Although it was suggested as early as 1968 (Brady et al., 1968) that fingernails might be useful for after-the-fact dosimetry, only recently have the necessary studies been carried out to demonstrate convincingly that this approach has potential for use in the field for triage and perhaps even fairly precise determination of dose. Preliminary results indicate that using simple cuttings from fingernails and X-band (9500 MHz) for the measurements, absorbed doses as of 1 Gy with an uncertainty of ±0.50 Gy (1 SD) can be obtained with currently available techniques and instruments (Romanyukha et al., 2007; Trompier et al., 2007). If the use of fingernails for field dosimetry continues to develop, there should be no difficulty in constructing a field-deployable 9500 MHz spectrometer for this purpose, which would be lightweight and automated for use by minimally trained individuals. The radiation-induced signals in fingernails are stable for at least several days (and much longer if the samples are collected within a few hours after the event and stored at low temperature).

Because the measurements would be made in vitro, it should be possible to calibrate the radiation response of each sample by a simple procedure in which radiation is added to the sample. A potential advantage of measurements in fingernails, especially if combined with in vivo EPR dosimetry of teeth, include obtaining the measurement from a different location on the body (thereby providing a means to assess if there was an heterogeneous exposure).

Potential limitations to this approach may be overcome by simple modification of the collection process. For example, cutting of the fingernail can create a mechanically induced signal (MIS) that overlaps with the radiation-induced signal (RIS). However, the MIS decays rapidly and the decay is greatly accelerated by simple chemical treatment. The influence of this MIS also can be removed by appropriate data processing because the shape is different from the RIS. As is the case with any technique that requires removal of a sample from the subject, there is a potential for mislabeling the sample. This problem can be reduced by the development of automated procedures

to rapidly remove any MIS and, if necessary, to calibrate the individual sample. Because only minimal manipulation of the sample is required and the measurement can be made within 5 min, it is feasible to determine the absorbed dose while the subject is still present. Finally, this method may not be applicable in children where nail volume is low.

2.2.3. Measurements in "biopsies" of teeth using 9500 MHz EPR

Many studies have demonstrated that retrospective measurements of dose by examination of isolated teeth with higher frequency EPR can provide very accurate estimates of dose at times ranging from immediately after the exposure to archeologically relevant times (Desrosiers and Schauer, 2001). The practical problem with this approach for acute dosimetry is the need to remove the tooth from the mouth. It now appears feasible, however, to obtain small samples from teeth rapidly and in a cosmetically acceptable manner. Small amounts can be used because of the increased sensitivity of higher frequency EPR and, there may be advantages in using frequencies even higher than 9500 MHz. Such a process could be very useful for triage and early assessment of dose to help in the determination of therapeutic intervention. Even if the technique of tooth biopsy does not fully meet the expectations, there may be situations where the value of the information that would be obtained would justify the removal of a tooth for in vitro measurement. The latter approach might be applicable in subjects for whom there are other indications of a potentially life-threatening dose and it is essential to verify the dose so that potentially risky therapies can be applied appropriately.

2.3. Other approaches and technologies

A variety of techniques and human samples have been used for diagnostic purposes in clinical medicine and forensics and offer opportunities for use in estimating acute radiation dose. A Joint Interagency Working Group on Emergency Biodosimetry (JIWG, 2005) recently developed a roadmap for development of key near-term and longer-term technologies with potential value for absorbed dose estimation.

2.3.1. Clinical signs and symptoms

Depending on the radiation dose, clinical signs and symptoms appear within hours to weeks after exposure to radiation. As shown in Fig. 1, the relative severity of signs and symptoms correlates in general with radiation dose. Although there are no radiation-specific clinical findings, the pattern of signs and symptoms in the setting of potential exposure should be recognizable by first responders and health care providers (Fliedner et al., 2001; Dainiak, 2002; Dainiak et al., 2006). The key potential limitation for their use in triage is the time that is required before these are manifest. See Appendix Materials (Acute Radiation Syndromes) for additional details related to clinical signs and symptoms as well as the use of hematological biomarkers (i.e. lymphocyte cell counts and depletion kinetics) for dose assessment.

2.3.2. Neutron activation

The radiation field may also have a neutron component (e.g. neutron source or critical assembly). Methods used for triage of victims of criticality accidents can be easily extended to a large number of individuals. A rapid and efficient triage can be performed by the measurement of sodium activation in humans. Thus, in the field, a very short measurement performed with a simple gamma survey instrument positioned against the umbilicus is a good indicator of the severity of neutron exposure (Delafield, 1988). Sodium activity can be measured again more precisely at a later stage using a whole-body counter. Moreover, measurements of sulfur activation in nails or hair and sodium activation in blood performed in a medical lab can also provide accurate estimation of neutron dose and information on dose heterogeneity (Hankins, 1980). These neutron activation measurement techniques are operational in all nuclear Centers with a risk of criticality accident. Procedures and protocols have been established for several decades and some countries offer the possibility of regular training of interventional teams and medical analysis laboratories (Médioni et al., 2004).

2.3.3. Molecular markers in body fluids and tissues

Molecular markers (biomarkers) reflect underlying changes in physiology which can arise from physical damage (e.g. cell lysis and the release of intracellular proteins into the circulation, oxidation by-products or DNA breakage), underlying changes in biochemistry (e.g. presence of new metabolites or changes in levels of key gene products), and/or changes in cellular composition of tissues. They include molecules as diverse as proteins and small molecule metabolites. New research with genomic- and proteomic-wide tools is showing that within minutes to hours after exposure to ionizing radiation proteins are modified and activated, and large-scale changes occur in gene expression profiles involving a broad variety of cell-process pathways (Amundson et al., 1999; Park et al., 2002; Blakely et al., 2002a, b; Kang et al., 2003; Yin et al., 2003; Ménard et al., 2006). There are presently approximately 90 known proteins that show changes in expression or undergo post-translational modifications after exposure to ionizing radiation. Some of these change in a dose dependent fashion although there are limited data on the shapes of dose– and time–response curves. The wealth of information generated by these studies provides a promising foundation for developing mechanism-based biosignatures of exposure that correlate with the timing and absorbed dose (Chen et al., 1973; Becciolini et al., 1987; Horneck, 1998; Bertho et al., 2001; Grace et al., 2002, 2003, 2005; Blakely et al., 2002a, b, 2003a, b; Amundson et al., 2004). While this approach currently is at an early stage of development for applications to triage for mass casualties, this is an exciting and potentially valuable approach, which might include assays that would be implementable in the field.

2.3.4. Luminescence

Radiation-induced stimulatable luminescence of a wide variety of natural and manufactured materials has been studied since the early decades of the 20th century. Although initial
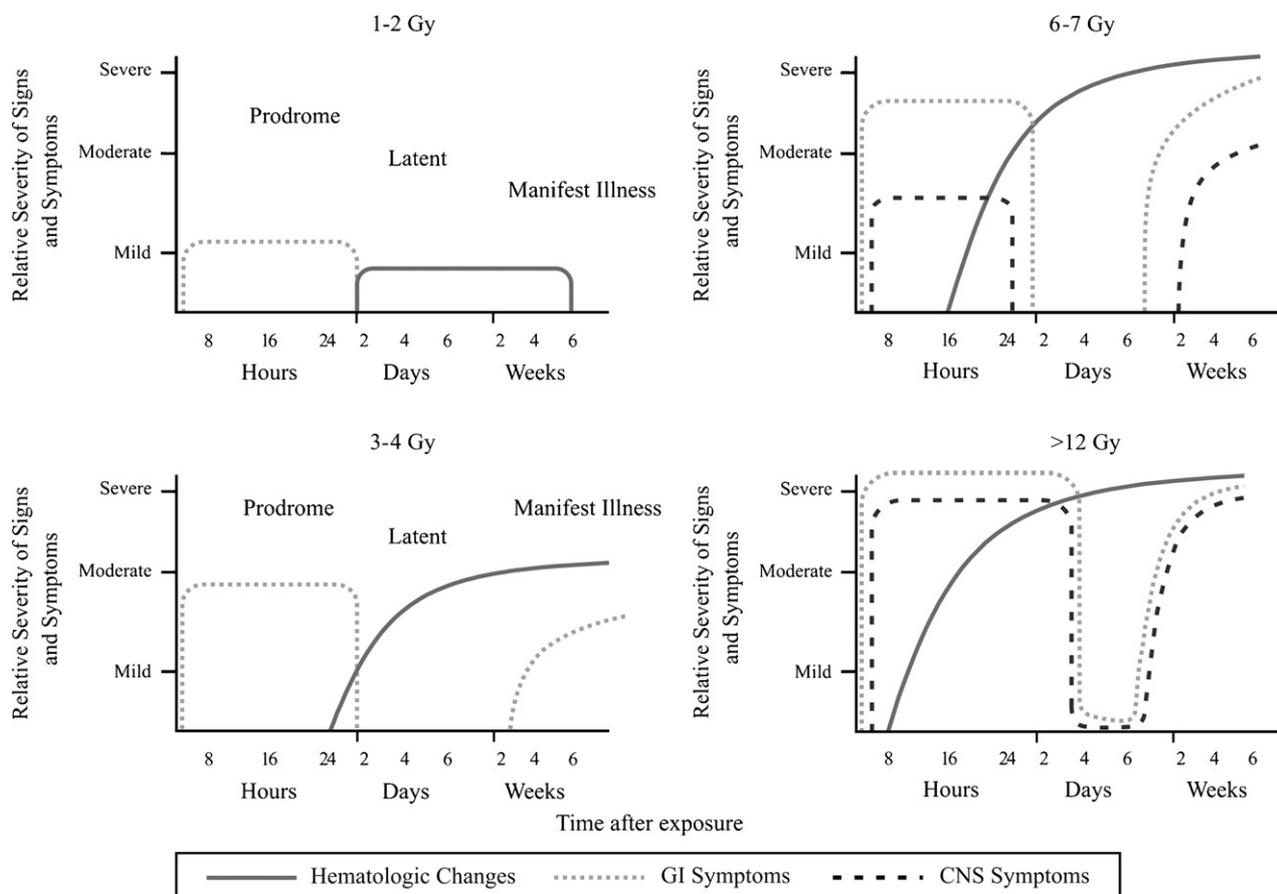
Fig. 1. Approximate time course of clinical manifestations. Shown are approximate times for hematopoietic, gastrointestinal (GI), and central nervous system (CNS) symptoms at different dose ranges of dose of whole-body exposure. Hematopoietic changes include development of lymphopenia, granulocytopenia, or thrombocytopenia. Gastrointestinal symptoms include headache, nausea, vomiting, or diarrhea. Cerebrovascular signs and symptoms include headache, impaired cognition, disorientation, ataxia, seizures, prostration, and hypotension. Note that the signs and symptoms of different organ systems significantly overlap at each radiation dose and that cerebrovascular symptoms do not appear until exposure to a high whole-body dose. The relative severity of signs and symptoms is measured on an arbitrary scale (AFRRI, 2003).

research was focused on the chronology and authentication of archaeological objects, the methodologies are suitable for the detection of very low absorbed doses. In these techniques, luminescence is stimulated either thermally as in thermoluminescence (TL), or optically (OSL) using either infrared or visible photons (Huntley et al., 1985; Aitken, 1985; Bøtter-Jensen et al., 2003). With presently available technology, it is estimated that a dose of 15 Gy should be readily detectable using whole teeth (Godfrey-Smith and Pass, 1997). Much lower detection limits (i.e. ∼ 1 Gy) should be possible with additional research to optimize such factors as excitation wavelength, its incident intensity, spectral width of the detection band, and the sample-to-detector geometry. In addition to applying luminescence to measure absorbed dose directly in a human, the technology also offers promise to indirectly assess radiation dose using "fortuitous" materials. A number of common materials often in the possession of humans or nearby that can serve as dosimeters for evaluating absorbed dose. Göksu (2003) showed that doses as low as 250 mGy can be measured on chipcards by infrared stimulated luminescence (IRSL). As chipcards are widely distributed (e.g. credit cards and mobile phones), this

work demonstrated convincingly that this approach has great potential for population triage since measurements can be made rapidly with a semi-automatic reader. Some of these methods have been used in the reconstruction of doses to A-bomb survivors with, for example, tile and brick, heated to produce TL (RERF, 1983). Absorbed doses from 0.01 to 1 000 Gy have been measured using untreated table salt (Kaibao et al., 1986). Absorbed doses from X-rays, Gamma rays and β particles can be measured in any material that stores energy from ionizing radiation as unpaired electrons trapped in an elevated energy state.

2.3.5. Ultrasound

Medical injuries from a nuclear detonation or conventional explosive contaminated with radionuclides are likely to involve thermal trauma in addition to radiation injury (combined injury). A high-frequency ultrasound technique has been developed to function as a clinical tool to distinguish partial-thickness from full-thickness thermal burns (Roswell et al., 1977; Goans and Cantrell, 1978; Cantrell et al., 1978). This technique could be extended to analyze radiation-induced injury. Ultrasound analysis may provide invaluable assistance in

the identification of people who have received absorbed doses below some established level of threshold. This is of great importance if many people are assumed to be significantly exposed and medical triage must be administered. Resolution of soft-tissue damage has been shown to be less than 0.2 mm. Two pilot studies indicate that both pulse-echo ultrasound and standard B-scan ultrasonic imaging are sensitive to high-level radiation-induced cutaneous damage (Personal communication, Dr. R.E. Goans, Health Physics Midyear Symposium in New Orleans, LA). The sensitivity of the technique for measuring pathology is at least as great for radiation injury as for thermal injury.

2.3.6. Breath gas analysis

Another promising area for biological measures of radiation injury is breath analysis. The vast majority of tissue damage following irradiation results from the action of free radicals produced by the absorption of ionizing radiation. Free radical-induced damage is associated with the process of lipid peroxidation of omega-3 and omega-6 fatty acids (Sies, 1997). End products of lipid peroxidation of polyunsaturated fatty acids are ethane and pentane. Breath ethane generation was measured by Arterbery et al. (1994) during clinical total-body irradiation for treatment over a 4-day period and changes in breath ethane were correlated with clinical manifestations of gastrointestinal side effects. More recent studies suggest greater sensitivity is possible (Mueller et al., 1998; von Basum et al., 2003). These studies suggest the possibility of breath analysis as a tool to support triage following exposure to radiation. However, these gases are associated with a variety of medical conditions that may complicate future attempts to use breath analysis to estimate absorbed radiation dose.

2.3.7. Non-quantitative biodosimetry measurements

Biodosimeters can be divided into those that measure absorbed dose and those that are semi-quantitative estimators of absorbed dose. Less studied but in some respects quite important are the non-quantitative biological responses assays. Non-quantitative biodosimetric techniques are those that have an absorbed dose response, but which are not consistently expressed in all subjects. There is a proliferation of such assays which include metabolomic assays, some of which are already appreciated as potential tools for distinguishing exposed subjects from the concerned public (worried well) (Barrett et al., 1982; Becciolini et al., 1984; Junglee et al., 1986; Straume et al., 1992; Chen et al., 2001, 2002). These assays are typically non-specific for radiation exposure, but they can be very organ specific. Additionally, clinical signs and symptoms following radiation exposure may provide a type of dosimetry that is very relevant to clinical management. Ultimately biodosimetry, for the purpose of epidemiology or triage, critically depends on the availability of paired measurements of quantitative dose (preferably physical dose) along with semi- and non-quantitative measures.

Techniques for scoring of non-quantitative radiation effects are commonly performed in the oncology community, where these non-quantitative biodosimeters are defined as treatment related toxicity. Scoring systems for side effects in therapeutically irradiated subjects have been compiled, and are in international use. The most recent and comprehensive of these systems is the CTCAE v. 3.0 (Chen et al., 2006; CTEP, 2006; Trotti et al., 2003) and before that was the LENT/SOMA system (Anacak et al., 2001; Rubin et al., 1995). The spectrum of late radiation effects differ between the therapeutic- and accidental-exposure populations, and a standard scoring system geared to the accidentally exposed population has been proposed (Waselenko et al., 2004). Non-quantitative biodosimetry will likely prove to be a critical component of epidemiology and triage and, therefore, deserves further study.

3. Recommendations and summary

No single assay is sufficiently robust to address all potential radiation scenarios including management of mass casualties and diagnosis for early medical treatment. The Acute Dosimetry Consensus Committee's recommendations involve use of a multi-parameter biodosimetric strategy that is presented for use by first responders/first receivers in the framework of three distinct radiological scenarios including: (a) radiation exposure device (RED), (b) radiological dispersal device (RDD), and (c) an improvised (or otherwise acquired) nuclear device (IND) after the radiological incident (Table 2).

This consensus-based document provides guidance to obtain emergency response dosimetry information in the event of a radiological incident to support medical triage for possible life-saving intervention of radiation overexposure. Consensus protocols for various recommended acute

Table 2
Acute-phase patient assessment information

Assessment method
Direct recording of location history
Direct observation of clinical signs and symptoms
Personal monitoring (direct, non-invasive)
In vivo EPR
Portable hand-held meters (triage/screening)
Portal monitors (triage/screening)
Whole-body counting
Personal monitoring (indirect, invasive)
Blood chemistry (i.e.amylase activity)
CBC and differential/lymphocyte count
Cytogenetics
In vitro EPR
Nasal swab
Stool sample
Urine sample (spot or 24 h)
Area monitoring
Dosimetry results (e.g. TLDs, aerial measurements) combined with personal location information

The top two priorities in acute-phase patient assessment are recording the patient's location history and observing clinical signs and symptoms. Note that the personal and area monitoring methods are listed in alphabetical order and, therefore, their location in the table does not infer priority or preference.

dosimetry protocols were developed for: (a) medical record-ing (e.g. biodosimetry worksheet, see website http://www.afrri.usuhs.mil/www/outreach/pdf/afrriform331.pdf, (b) bioassay sampling for radioactivity assessment, (c) nail-clipping sampling for EPR analysis, (d) blood collection for hematology, cytogenetics, and blood chemistry analyses, and (e) in vivo EPR analysis. To our knowledge this is the first time that global biodosimetric protocols for acute dosimetry were assembled for use by first responders/first receivers.

The sampling protocols given in this document are considered to be a best practices approach and are intended for use as a technical basis document for emergency response procedures. Individual states or facilities can adapt these recommendations to their specific source terms, credible events and organizational structure to the extent applicable.

Appendix A contains the US FDA's guidance for review of devices and guidance for "emergency use" of unapproved devices. This information is provided as an example of federal regulatory requirements; similar guidance can be obtained from other regulatory bodies around the world.

We acknowledge that due to the dynamic developments in this area, these recommendations from a committee of experts during the BiodosEPR-2006 meeting will need to be reassessed and updated on a recurring basis. It is recommended that this assessment be performed biennially.

Acknowledgments

Appendix A. Review of medical devices for dose assessment by the US Food and Drug Administration

A number of devices are currently available or under development, or have been identified as desirable for future development in the assessment of absorbed dose and the physiologic effects from radiation exposure. To the extent that these devices would be used as part of a multi-parameter approach for medical management, including diagnosis and therapeutic decision-making, they very well might need to be reviewed by the US Food and Drug Administration (FDA) for approval for investigational clinical use in a pre-market setting, and/or for marketing approval following clinical trials. FDA's Center for Devices and Radiological Health (CDRH) reviews medical devices for safety and efficacy prior to marketing, monitors these devices throughout the product life cycle, including post-marketing surveillance, and ensures that radiation-emitting products meet radiation safety standards.

FDA and CDRH websites contain extensive information on the device review and approval processes, including searchable databases for regulations, guidance documents and publicly releasable information on existing applications. Manufacturers, investigators and other interested parties are encouraged to consult these websites to help guide them through the regulatory process. Some examples of particularly useful web links are found at:

> http://www.fda.gov/opacom/hpview.html (About the US Food and Drug Administration),
> http://www.fda.gov/oc/industry/default.htm (Information for FDA-Regulated Industry),
> http://www.fda.gov/cdrh/devadvice (Device Advice).

Manufacturers are further encouraged to consult with the FDA as early as possible in the product development process and certainly before the submission of an investigational device exemption (IDE), which is required to conduct a clinical trial. FDA is open to communication with sponsors and offers both informal and formal guidance meetings to discuss and come to agreement on the details of an investigational plan. For more information on the IDE process, please consult:

> http://www.fda.gov/cdrh/devadvice/ide/index.shtml (IDE),
> http://www.fda.gov/cdrh/ode/idepolcy.html(Guidance on IDE Policies and Procedures),
> http://www.fda.gov/cdrh/ode/guidance/310.pdf (Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff).

Medical devices which were brought to the market prior to May 28, 1976 (i.e. the date of enactment of the Medical Device Amendments) were "grandfathered" for marketing approval. Those devices which were grandfathered were later classified into three groups. Class I devices are those for which only "general controls" are required to provide reasonable assurance of safety and effectiveness. These devices are generally not life-supporting or life-sustaining and pose minimal risk of illness or injury. Class II devices are those which require special controls such as performance standards, postmarketing surveillance or patient registries to ensure safety and efficacy. Class III devices require the submission of a pre-market approval (PMA) application due to their life-supporting/life-sustaining nature and the potential for unreasonable risk of illness or injury. "New" devices which fall into Class I or II may be marketed without a PMA, so long as they are deemed to be substantially equivalent to a device which was marketed prior to May 28, 1976. A 510(k) application is required (21CFR Part 860) for FDA to assess whether the new device is substantially equivalent to a pre-Amendment device or a device that is currently legally marketed.

Please consult: http://www.fda.gov/cdrh/devadvice/314.html (Premarket Notification 510(k)).

Expanded access: FDA may make unapproved devices available to the medical community on an "emergency" basis under the Expanded Access provisions of the FDA Modernization Act of 1997 (Section 561 of the Food, Drug and Cosmetic Act). These provisions allow for the use of unapproved devices under certain conditions including:

1. the patient has a life-threatening condition that needs immediate treatment;
2. no generally acceptable alternative treatment exists for the condition; and
3. because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval.

Treatment use: FDA will also consider the treatment use of an investigational device as a way of facilitating the availability of promising new therapeutic and diagnostic devices to desperately ill patients as early in the device development process as possible (prior to marketing) and to obtain additional safety and efficacy data.

Under the final rule (62 FR 48940, September 18, 1997), treatment use of an investigational device will be considered when:

1. the device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
2. there is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population;
3. the device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed; and
4. the sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence.

A.1. Emergency use authorization

The following are excerpts from the Draft Guidance "Emergency Use Authorization of Medical Products; Availability" (reference provided at the end of this section).

Under Section 564 of the FD&C Act (the Act), as amended by the Project BioShield Act of 2004, the Commissioner of FDA may authorize the emergency use of a drug, device or biological product which is not approved, cleared or licensed under Sections 505, 510(k) or 515 of the Act or Section 351 of the PHS Act provided there has been a declaration of a domestic, military or public health emergency by the Secretary of Homeland Security, Defense or Health and Human Services, respectively.

The FDA Commissioner may issue an EUA only if, after consultation with the Director of NIH and the Director of CDC (to the extent feasible and appropriate given the circumstances of the emergency), the FDA Commissioner concludes that:

1. the agent specified in the declaration of emergency can cause a serious or life-threatening disease or condition;
2. based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing—(a) the serious or life-threatening disease or condition referred to in paragraph (1); or (b) a serious or life-threatening disease or condition caused by a product authorized under Section 564, or approved, cleared, or licensed under the FD&C Act or PHS Act, for diagnosing, treating, or preventing the disease or condition referred to in paragraph (1) and caused by the agent specified in the declaration of emergency;
3. that the known and potential benefits outweigh the known and potential risks of the product when used to diagnose, prevent, or treat the serious or life-threatening disease or condition that is the subject of the declaration; and
4. that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such serious or life-threatening disease or condition.

Although an EUA may not be issued until after an emergency has been declared by the Secretary, FDA recognizes that during such exigent circumstances, the time available for the submission and review of an EUA request may be severely limited. Therefore, the Agency strongly encourages an entity with a possible candidate product, particularly one at an advanced stage of development, to contact the FDA Center responsible for the candidate product even before a determination of actual or potential emergency. This draft guidance offers recommendations for both "pre-emergency" activities to be conducted prior to the determination of actual or potential emergency and "emergency" activities to be performed once the determination has been issued. In addition, this section of the draft guidance sets out the types of information FDA believes are important to allow an assessment of safety and effectiveness and to make an adequate risk–benefit determination to support issuance of an EUA.

Pre-emergency activities: Such activities may include discussions with FDA about a prospective EUA product and the appropriate vehicle to use, such as an IND, IDE, or Master File, when submitting data on the product prior to a determination of actual or potential emergency. The Agency strongly recommends that an entity submitting data during a "pre-emergency" period follow the recommendations for data submission contained in "Submission of a Request for Consideration," below. If, prior to the declaration of an emergency, FDA believes that a candidate product may meet the criteria for an EUA, the Agency may share appropriate information on such product with the Secretary's EUA Working Group (WG).

Emergency activities: Once a determination of actual or potential emergency has been made under Section 564(b)(1), the Secretary may declare an emergency justifying the authorization to use an unapproved medical product or an approved medical product for an unapproved use. The Secretary will consult

with the EUA WG; other technical experts from FDA, NIH, and CDC; and other agencies and private entities, where appropriate, to identify products that may be eligible for an EUA in light of the circumstances of the emergency and to facilitate timely submission of the EUA request by an appropriate entity.

Submission of a request for consideration: Section 564(c) requires that the data to support authorization demonstrate that, based on the totality of scientific evidence available to the FDA Commissioner (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition. The exact type and amount of data needed to support an EUA may vary depending on the nature of the declared emergency and the nature of the candidate product. To facilitate FDA review of such data, the Agency recommends that a request for consideration for an EUA include a well-organized summary of the available scientific evidence that evaluates the product's safety and effectiveness, including the adverse event profile when used for diagnosis, treatment, or prevention of the serious or life-threatening disease or condition, as well as data and other information on safety, effectiveness, risks and benefits, and (to the extent available) alternatives.

The text below summarizes the types of data that FDA recommends be submitted to support a request for consideration for an EUA.

Summary of recommended data to support a request for consideration: For FDA to evaluate a request for consideration for an EUA, the Agency recommends that the following information be submitted:

1. a description of the product and its intended use (e.g. identification of the serious or life-threatening disease or condition for which the product may be effective);
2. identification and an explanation of what unmet need(s) would be addressed by issuance of the EUA;
3. a description of the product's approval or clearance status, if any, under the FD&C Act or licensure status under the PHS Act, and whether the product is under an investigational application (e.g. whether the product is unapproved or whether it is approved but the EUA is for an unapproved use; whether an IND or IDE is in effect or has been submitted); whether the product is licensed for either the proposed or another use in a foreign country; information on the use of the medical product by either a foreign country or an international mutual defense organization such as NATO;
4. a list of each site where the product, if authorized, would be (or was) manufactured and the good manufacturing practices (GMP) status of the manufacturer;
5. identification of any approved alternative products, including their availability and adequacy for the proposed use (if known);
6. available safety and effectiveness information for the product;
7. a discussion of risks and benefits;
8. a description of the information for health care providers or authorized dispensers and recipients of the product, (e.g.

two separate "Fact Sheets"), and the feasibility of providing such information to health care providers or authorized dispensers and recipients in emergency situations;
9. information on chemistry, manufacturing, and controls;
10. instructions for use of the EUA product (e.g. if follow-up treatment is required); and
11. proposed labeling (if applicable).

More detailed information regarding Emergency Use Authorization may be obtained in the Draft Guidance published in the Federal Register as follows:

Vol. 70 (July 5, 2005): Docket No. 2004D-0333, OC 200461. Draft Guidance; Emergency Use Authorization of Medical Products; Availability. Pages 38689–38692 [FR Doc. 05-13121] or at the following website: http://www.fda.gov/oc/bioterrorism/emergency_use.html.

Appendix B. Current practice of CB for radiation incidents and accidents

Prior to 1960 medical management of radiation incidents relied on the history of the event, health physics studies, time and motion simulation, and analysis of any available dosimeters to determine the absorbed dose. Additionally, medical management was heavily weighted toward clinical response to the evolution of various syndromes characteristic of the ARS, or of acute local cutaneous injury. Since the period 1960s, the DA has been extensively developed and harmonized to international standards (IAEA, 2001; ISO, 2004). Treating physicians now have the ability to ascertain the relative magnitude of the incident relatively quickly. In addition, studies indicate that the likelihood of survival can be significantly increased with appropriate aggressive medical intervention and care (Anno et al., 2003).

Since the terrorist attack of 9/11/2001, potential radiation exposure scenarios now include detonation of nuclear weapons, terrorist attacks on nuclear reactors, covert placement of large sources in public places, and dispersal of radioactive substances with the use of conventional explosives (Mettler and Voelz, 2002). Lack of availability or inaccurate initial absorbed dose estimates can result in suboptimal medical intervention. In the acute phase after a radiation incident, it has been previously recommended that medical personnel rely heavily on clinical signs, lymphocyte kinetics, time to emesis, and chromosome biodosimetry (Goans, 2002; Goans and Waselenko, 2005). However, every dose indicator has limitations and a multi-parameter triage schema has been proposed to obtain the best immediate statistical evaluation of dose (Blakely et al., 2005). These techniques have been computerized for use on a laptop computer (BAT, Biodosimetry Assessment Tool, AFRRI, www.afrri.usuhs.mil) and, recently, for use of a beta-version on a hand-held personal digital assistant (PDA).

The conventional lymphocyte metaphase-spread DA has been applied in the clinical management of several overexposure accidents. In addition, the PCC assay has been found useful at various dose levels. Conventional metaphase-spread chromosome-aberration biodosimetry techniques are robust,

Table 3
Cytogenetic biodosimetry techniques as a function of dose[a]

Dose range (Gy)	Proposed validated dosimetry method	Prodromal effects	Manifest symptoms	Survival expectancy
0.1–1	Dicentric/PCC-CHO	None to mild (1–48 h)	None to slight decrease in blood count	Expected survival
1.0–3.5	Lymphocyte depletion kinetics/dicentrics/PCC-CHO; amylase dose response analysis; C-reactive protein (CPR) assay	Mild to moderate (1–48 h)	Mild to severe bone marrow damage	0–10% death
3.5–7.5	Lymphocyte depletion kinetics/PCC-ring; C-reactive protein (CPR) assay	Severe (1–48 h)	Pancytopenia, mild to moderate GI damage	10–100% death within 2–6 weeks
7.5–10.0	Lymphocyte depletion kinetics/PCC-ring	Severe (< 1–48 h)	Combined BM and GI damage	90–100% death within 1–3 weeks
> 10.0	PCC-ring	Severe (minutes to < 48 h)	GI, neurological, cardiovascular damage	100% death (within 2–12 days)

[a] Adapted from Prassanna et al. (2005).

but they are laborious and time-consuming. In addition, for potential high-dose irradiation above the median lethal dose, it is expected that radiation-induced cell death and delay in cell-cycle progression into mitosis will interfere with dose estimation. In order to overcome this limitation, quantitative analysis of radiation-induced damage may be performed using resting peripheral lymphocytes *in lieu* of metaphase spreads. Use of interphase cytological assays, such as the PCC assay, can eliminate these inherent problems associated with the use of metaphase-spread cytogenetic assays. The PCC assay is useful to determine exposure to low doses as well as to life-threatening acute high doses of low- and high-LET radiations (Prasanna et al., 1997). In addition, the PCC assay can discriminate between total- and partial-body exposure (Darroudi et al., 1998; Blakely et al., 1995). The rapid interphase chromosome aberration (RICA) assay is a simple alternative to the metaphase-spread-based DA. In the RICA assay, damage involving specific chromosomes is analyzed in chemically induced PCC spreads after FISH with specific whole-chromosome DNA hybridization probes (Prasanna et al., 2000).

Recently, it was suggested that the DA could be adapted for the triage of mass casualties (Lloyd et al., 2000; Voisin et al., 2001; Prasanna et al., 2003). Lloyd et al. (2000) described an in vivo simulation of an accident with mass casualties receiving whole- or partial-body irradiation in the 0–8 Gy range. Faced with an urgent need for rapid results, clinical triage was accomplished by scoring as few as 20 metaphase spreads per subject, compared with the typical 500–1000 spreads scored in routine analyses for estimating absorbed dose. However, Lloyd et al. (2000) suggested increasing the analyses to 50 metaphase spreads when there is disagreement with the initial assessment or when there is evidence of significant inhomogeneous exposure.vskip1pt

After the initial results are communicated to the treating physician, additional scoring is recommended to resolve poten-

tial conflicts in dose assessment and, in the case of high dose, to assist physicians considering marrow-stem-cell transplantation to mitigate bone marrow ablation. Using the DA in this triage mode, a reasonable throughput of 500 or more samples per week per laboratory is achievable (Prasanna et al., 2003).

Table 3 lists current recommendations (Prassanna et al., 2005) on the type of CB to use when a preliminary estimate of dose has been obtained.

Appendix C. Current status of deployable mitigating agents

A consensus conference on the preparedness for haematological and other medical management of mass radiation accident was held at Vaux de Cernay Abbey (France) in October 25–27, 2005, under the auspices of the European Cooperative Group for Blood and Marrow Transplantation (EBMT), the Institute for Radioprotection and Nuclear Safety (IRSN, France), and the University of Ulm (Germany). A working group consisting of 65 physicians and health ministry representatives from the 25 EU countries with specialists in the field of haematology, radiopathology and dosimetry, achieved a consensus regarding early management of casualties resulting from a large radiological accident or a terrorist attack (Gorin et al., 2006). Their recommendation was that cytokine therapy should be used for treatment of cytopenia caused by irradiation. This recommendation is consistent with a consensus opinion expressed by the Strategic National Stockpile Radiation Working Group (Waselenko et al., 2004).

Early identification of significant damage to the bone marrow and other organs by biodosimetric techniques could allow early treatment of bone marrow with cytokines (G-CSF, GM-CSF, and others). Early cytokine therapy may lead to improved survival, based on large animal studies (MacVittie et al., 2005). Cytokines are not currently approved by the FDA for treatment of radiation-induced injury. However, current thinking is based on results in animal models showing that treatment with

cytokines within 24 h, or as soon as possible after significant bone marrow depression is identified, may improve survival. Depending on the preparation, cytokines may be administered by subcutaneous injection. This route of administration is considered to be safe, if there is bone marrow depression. Additionally, surgical repair of severe injuries should be performed as soon as possible, even within the first 24 h, while neutrophils still remain in circulation. The higher the absorbed dose received, the more important it is that early treatment with cytokines be administered and that early surgical treatment be attempted.

In a mass-casualty scenario, hospitalization is usually unnecessary in the first 24 h following administration of cytokines for a moderate absorbed dose in the survivable range (i.e. < 7 Gy), unless accompanied by a treatable injury or a very high absorbed dose. Supportive care, including the use of antimicrobial agents, fluid and electrolyte replacement, volume resuscitation, transfusion with leukoreduced, irradiated blood products and comfort measures (such as analgesics, anxiolytics and/or sedatives) should be administered within the first few days after exposure.

Appendix D. Bioassay sampling for radioactivity

D.1. Urine (spot) collection procedure for radionuclides bioassay

Urine collection (*spot*): Urine collection cups (standard 100–120 ml) with screw caps are recommended to minimize leakage during handling and shipment.

Instruct each person to do the following for urine collection:

- wash hands with soap and water;
- remove the cap from cup when ready to void;
- collect at least 60 ml urine in the cup in a non-contaminated area;
- do not touch the inside of the cup or cap at any time;
- recap the specimen and deliver to the person in charge; and
- label *urine container* with *participant ID* and *collection date*.

After collection, recap the urine cup *making sure the cap is tight*.

Urine storage (*before shipment*): Store the urine cups in a freezer (-20 or $-80\,°C$) immediately after collection. If a freezer is not available, place in a refrigerator until shipment.

Shipping list: Include a copy of the sample IDs in the shipping container (underneath the lid) when shipping specimens to the laboratory.

Shipping procedure: The urine cups should be placed inside a zip-lock bag along with absorbent material. The absorbent material should be capable of absorbing at least 500 ml of fluid. Freeze the urine cups before placing them in the shipping container. Pack the cups in an upright position in the shipping container.

Securely place the urine cups in the bottom of the shipping container. Place a layer of newspaper, bubble wrap or other packing material between the specimens and the dry ice. Add at least 10 lbs of dry ice to the shipping container. Depending on the number of samples more dry ice may be needed. Any additional space in the shipping container that is not taken up with dry ice or specimen boxes should be filled with bubble wrap, newspaper, etc. to prevent the movement of specimen boxes during the shipment. After filling the shipping container, cover with a Styrofoam lid and tape down the cardboard outer flaps. Place a dry ice label on the outside of the container and write in the amount of dry ice in the shipping container.

If dry ice is unavailable, use "cold packs" so that the urine stays cold during the shipment to the laboratory.

See the web site below for proper shipping instructions. www.bt.cdc.gov/labissues/pdf/chemspecimenshipping-urine.pdf.

D.2. Urine collection (24 h) procedure for radionuclides bioassay

Urine collection (*24 h*). Urine collection container (standard 2000–3000 ml) with a disposable funnel.

Instruct each person to do the following for urine collection:

- wash hands with soap and water;
- remove the cap from the container when ready to void;
- collect all of the urine for 24 h in a non-contaminated area;
- store the urine in a refrigerator or freezer during collection (to control bacterial growth);
- do not touch the inside of the container or cap at any time;
- at the end of the collection cap the container well deliver to the person in charge; and
- label *urine container* with *participant ID* and *collection date*.

After collection, recap the urine container *making sure the cap is tight*.

Urine storage (*before shipment*): Store the urine container in a refrigerator immediately after collection until shipment.

Shipping list: Include a copy of the sample IDs in the shipping container (underneath the lid) when shipping specimens to the laboratory.

Shipping procedure: The urine containers should be placed inside a zip-lock bag along with absorbent material. The absorbent material should be capable of absorbing at least 3000 ml of fluid. Pack the containers in an upright position in the shipping container.

Securely place the urine containers in the bottom of the shipping container. Place a layer of newspaper, bubble wrap or other packing material between the specimens and the cold packs. Add several cold packs to the shipping container. Any additional space in the shipping container that is not taken up with dry ice or specimen containers should be filled with bubble wrap, newspaper, etc. to prevent the movement of specimen boxes during the shipment. After filling the shipping container, cover with a Styrofoam lid and tape down the cardboard outer flaps.

D.3. Nasal swabs collection procedure for radionuclides bioassay

Nasal swabs collection: Nasal swabs (standard applicator cotton or polypropylene) with a container.

Instruct each person to do the following for urine collection:

- wash hands with soap and water;
- moisten applicator with water or sterile saline solution;
- collect a separate applicator for each nostril;
- store the applicator in a culture tube or a glassine bag; and
- label the *containers* with *participant ID* and *collection date*.

Nasal swab storage (*before shipment*): Store the nasal swabs in a refrigerator or freezer immediately after collection until shipment.

Shipping list. Include a copy of the sample IDs in the shipping container (underneath the lid) when shipping specimens to the laboratory.

Shipping procedure: The nasal swab containers should be placed inside a zip-lock bag. Securely place the containers in the bottom of the shipping container. Place a layer of newspaper, bubble wrap or other packing material between the specimens and the cold packs. Add several cold packs to the shipping container. Any additional space in the shipping container that is not taken up with cold packs or specimen containers should be filled with bubble wrap, newspaper, etc. to prevent the movement of specimen boxes during the shipment. After filling the shipping container, cover with a Styrofoam lid and tape down the cardboard outer flaps.

D.4. Fecal samples collection for radiobioassay

(Adapted from Brooks US Air Force Laboratory—Institute of Environmental Health; See www.brooks.af.mil/afioh/Laboratories/sdrr_biological_samples.htm)

Fecal analyses are considered the most sensitive means of *in vitro* bioassay to detect inhalation or ingestion intakes of insoluble radionuclides, particularly transuranics such as americium, plutonium, thorium and uranium. As with urine samples, the sensitivity of the technique is highly dependent on the specific chemical form of the radionuclide, as well as the route of exposure. Even more important is the time between a suspected intake and sample collection. Since insoluble compounds pass through the GI tract rapidly post exposure, fecal samples should be collected within 5 days following a suspected acute intake. Sample in the following manner:

(1) Collect the specimen in a non-contaminated area, using precautions to avoid surface contamination of the collection container. This will include showering and washing hands prior to capturing the specimen.
(2) Defecate directly into a one gallon new plastic bag. Either zip-lock or a twist tie closure is acceptable.
(3) Seal the bag, and store in a cardboard carton.
(4) Repeat for all episodes in a 24 h period, placing each sample in the same cardboard carton. The sample may be kept cool or frozen during collection to control odor and bacterial growth.
(5) Properly identify the sample with name, SSN, collection start and stop dates, and a brief history or reason for sampling. Submit a completed biodosimetry worksheet (http://www.afrri.usuhs.mil/www/outreach/pdf/afrriform331.pdf) with the sample. Ship sample as soon as possible to the reference radiobioassay laboratory.

Appendix E. Provisional EPR biodosimetry protocols for use in radiation incidents and accidents

Nail clippings: Preliminary results indicate that EPR measurements of nail clippings may be used to assess absorbed dose > 1 Gy.

Information to be collected from the donors

- identity of the donor (name, age, gender, occupational activities);
- estimation of time elapsed since irradiation;
- estimation of donor position relatively to radiation source; and
- donor activities since irradiation (hand washing, shower, manual activities, sweating activities) (type, frequency, time).

Collection of nail clippings should be done according to the following instructions

- donors should not wash their hands;
- collect nail clippings as large as possible and with the minimum of cuts;
- collect separately nail clippings from fingers and toes, separate as well left and right;
- raw nail clippings can be directly stored without additional treatment in a small tube or container that can be sealed. No washing or cleaning;
- if possible, before sealing tube, weigh accurately each sample and report it;
- seal each container and store them at the lowest possible temperature and report time, temperature storage and storage device type; and
- variations of temperature during storage and transportation (time and temperature) should be reported.

Procedure for screening for the occurrence of potentially significant clinical exposures using in vivo EPR measurements of teeth in the mouth

A. Initial steps outside of magnet while in queue for measurements.

- Data pertinent to the patent entered (or transferred if data already obtained on the standardized biodosimetry work sheet).
- Resonator placed in mouth on tooth.
- Standard is in "inserted" position.
- Tooth diameter measured in two planes and data entered.

B. Procedures for measurement for the presence of clinically significant exposure.

- Subject positioned in the 400 gauss magnet.
- Acquire spectrum with standard setting standard in "inserted" position (confirmed by pushing "standard button", which initiates an automatic 10 s acquisition).
- Move standard to "not inserted position" via button marked "standard".
- Push button labeled "data acquisition", which starts data acquisition for (data usually obtained for approximately 5 min; other acquisition times can be preset by supervisor).
- Check that the readout has been entered into record automatically, giving dose and uncertainty associated with the measurement.
- If results indicate that the subject is in the category "potentially significantly exposed" (this level will have a default value of 2 Gy, based on the measured dose plus 1 standard deviation (SD); it can be adjusted at the request of the supervising authority to a different value) the subject is directed to designated site for subjects for further evaluation.
- If results indicate that the subject is not in the category "potentially significantly exposed" (e.g. the measured value +1 SD is < 2 Gy), this is entered into the record, the subject is informed, and subsequent steps (e.g. if further screening for confirmation is to be performed) taken as determined by the procedures established by the manager for the incident).

C. Procedures for more precise measurement of dose after the presence of a probable clinically significant exposure has been found.

- Procedure B is modified principally by increasing the acquisition time from 5 to 20 min (which will increase the ability to resolve the dose by a factor of 2). Longer time periods can be utilized to further enhance the resolution of dose.

Appendix F. Procedures for collecting blood for hematology, chromosomal, and blood chemistry analyses

Blood collection for hematology, chromosomal, and blood chemistry analyses should be performed by qualified medical personnel. To ensure successful application of these various blood-based biodosimetry tools, it is very important that the blood be collected and shipped according to protocol outlined below:

- Before the blood sample is taken notify the reference laboratory(s) representative so that they can prepare for its arrival and pick up.
- All blood samples are to be collected into designated blood tubes and volumes as shown in Table 4. Gently rock the tubes for 2 min to ensure proper mixing. Label the tubes unambiguously and complete the biodosimetry worksheet (http://www.afrri.usuhs.mil/www/outreach/pdf/afrriform331.pdf).
- Package the blood sample carefully to prevent breakage of the tubes in transit. Also, the blood should be maintained at

Table 4
Blood tubes and volumes for selected biodosimetric assays

Bioassay	Tube type	Blood volume (ml)
Hematology	EDTA tube	2
Cytogenetics	Lithium-heparin	10 (e.g. 2 × 5 ml)
Blood chemistry	Serum separator tube	2

about 20 °C. *Blood samples must not be frozen*. One method of maintaining blood at room temperature is to surround the tubes with gel packs that are at *room temperature*. To further ensure that the samples do not freeze during transportation (e.g. air-mail), mark on the external packaging and the shipping documents *Urgent Diagnostic Samples—not to be Frozen*. For air transport, packaging and labeling should conform to the current International Air Transport Association (IATA) regulations and Canadian Transport of Dangerous Goods (TDG) Regulations. *The UN for diagnostic specimens is UN3373*. These require that blood samples should be packed to conform to United Nations Regulation 602 for infectious materials. The package itself and the 'Nature and Quantity of Goods' box of the air waybill should show the following wording: "Diagnostic specimen packed in compliance with IATA packing instruction 650". Saf-T-Pak manufactures packaging that meets these requirements (STP 210) www.saftpak.com. Other packaging is acceptable providing it meets the requirements stated above.

- Mark the package and shipping documents '*Do not X-ray*'.
- Immediately after blood collection, ship the sample by *special transportation* and *use overnight air express so that the reference laboratory can receive the blood early in the morning following sample collection*. Contact the laboratory to confirm the shipment and inform them of the *waybill* number. *This is important for tracking the sample*.
- For best results blood must be received within 24 h of sampling.

Appendix G. Radiological exposure scenarios

Since the terrorist attack of 9/11/2001, the following potential radiation exposure scenarios have been identified: (a) use of a RDD, (b) RED, and (c) detonation of an IND or sophisticated nuclear weapon. See NCRP Commentary # 19 (NCRP, 2005) for additional details. While the generic procedures for medical management of radiation emergencies are the same whether for single or for mass nuclear or radiological casualties (IAEA, 2005), the consequences of malicious acts involving radioactive material, resulting in potentially large numbers of casualties, rapid depletion of medical resources, and limited personnel dictate a different medical management strategy for emergency response and use of biodosimetric assessment of radiation exposure.

Radiological dispersal device (*RDD*): A RDD uses conventional explosives or some other mechanism (e.g. sprayer) to spread radioactive contamination. One type of an RDD is commonly referred to as a "dirty bomb". RDDs are likely to

affect relatively small areas compared to a nuclear detonation. The immediate environment and persons in the area will become contaminated as the radioactive material is deposited on surfaces. Radiation exposures are expected both from external and internal contamination including possible radioactive shrapnel. The population impacted would be greater than for a RED, but would depend on the type of dispersal and radioactive material used (NCRP, 2005). It is highly unlikely that persons in the contaminated area will have medically significant levels of contamination, either external or internal, but fear and concern regarding personal safety may lead to psychological stress.

Radiation exposure device (*RED*): Sealed sources distributed in the environment generally do not present a contamination hazard. However, sealed sources can result in exposures to persons who come near an individual source and involve external exposure only. Persons who handle these sources may suffer significant local radiation injury to the skin and underlying tissues. Prolonged exposure to a high activity source could result in acute radiation syndrome and/or death. However, mass casualties are not expected when sealed sources are considered.

Improvised nuclear device (*IND*): An IND incorporates nuclear materials designed to produce a nuclear explosion. A nuclear detonation, with the resultant radiation, blast, and thermal injuries, would be catastrophic in comparison to the malicious acts described above; however, there still is need for medical triage (Yehezkelli et al., 2002). Hundreds to thousands of prompt fatalities are expected in the detonation zone, with an even greater number of persons with blast and burn injuries at a greater distance from the detonation zone. Fallout from these weapon detonations may lead to an even greater number of persons with significant levels of radiation exposure. Doses to the affected population will likely be due to both internal and external exposures. Medical resources will be quickly overwhelmed as most survivors will exhibit combined injuries from blast and thermal burns. The impact of radiation exposure will be secondary to medical management of conventional trauma. Early and late radiation health effects are potential consequences of an IND or nuclear event.

Appendix H. Acute radiation syndromes

A constellation of clinical findings appear in three distinct but overlapping phases of sequential events: the prodromal phase, the latent phase and the phase of manifest illness. In the "prodromal phase" some clinical signs and symptoms usually appear within the first 48 h after exposure, although they may be delayed for up to 6 days. The signs and symptoms include hematopoietic changes (especially a decline in lymphocyte count, absolute lymphopenia, granulocytopenia and/or thrombocytopenia), gastrointestinal symptoms (nausea, vomiting and/or diarrhea) and neurological symptoms (including headache, impaired cognition, disorientation, ataxia, seizures and hypotension). The "latent phase" lasts from approximately 2–20 days and is characterized by an improvement in symptoms. This apparent improvement gives the false impression that recovery is underway, although cytopenia typically per-

sists. The duration of the latent phase correlates inversely with absorbed dose (see Fig. 1). At low doses (1–2 Gy), overt early clinical symptoms may not occur.

The phase of "manifest illness" lasts from 2 to 60 days, during which time signs and symptoms occur due to injury of one or more organs. Immune suppression may be profound, predisposing to infection and sepsis. Patients who survive the phase of manifest illness are likely to recover from radiation injury. Individuals exposed to a radiation dose exceeding 10–12 Gy have a nearly 100% mortality.

Acute radiation syndromes occur after whole-body or significant partial-body irradiation of greater than 1 Gy, and consists of injury to one or more of four major organ systems: the gastrointestinal system, the neurovascular system, the hematopoietic system and the cutaneous system. The scope and severity of changes in each of these systems is summarized in Tables 5–7.

Hematopoietic syndrome: The hematopoietic syndrome develops at doses exceeding 1 Gy. The appearance of mild cytopenias without significant bone marrow damage characterizes a low level of hematopoietic toxicity (see Table 7). This correlates with an absorbed dose of less than 2 Gy. Peripheral blood lymphopenia may develop within the first 6–24 h after a moderate or high absorbed dose. The rate of decline and nadir of absolute lymphocyte count both correlate with cumulative absorbed dose (see Table 8) (Goans et al., 1997, 2001; Waselenko et al., 2004). A 50% decline in the absolute lymphocyte count within the first 24 h after exposure, followed by a further, more severe decline within 48 h, predict a potentially lethal exposure.

Individuals suffering from radiation injury combined with mechanical trauma and/or burns have a poor prognosis. Individuals with "combined injury" have a significantly poorer prognosis than individuals suffering from radiation injury alone.

Gastrointestinal syndrome: The appearance of mild gastrointestinal symptoms (i.e. 1 or 2 episodes of diarrhea, nausea, mild abdominal pain and late onset vomiting) typically is followed by complete recovery from radiation injury. Nausea and vomiting may be due to direct or indirect stimulation of centers within the central nervous system. The development of early onset vomiting (within 1–2 h), if known not to have a likely psychogenic origin, is a sign that prolonged medical intervention will be required. Together with a rapid rate of decline of the absolute lymphocyte count, the time to onset of vomiting has been used to estimate individual absorbed dose (see Table 8) (Waselenko et al., 2004). Accordingly, ⩾94% of individuals receiving an estimated dose of > 5 Gy develop vomiting within 1 h of exposure. Significant radiation injury (occurring at doses of ⩾5 Gy) results in impaired barrier function due to mucosal interruption and damage to the bowel wall. Such damage predisposes to infection by permitting passage of bacterial toxins through the intestinal wall into the bloodstream. Life-threatening complications include ileus ulceration, perforation, and necrosis of the bowel wall.

Neurovascular syndrome: The neurovascular syndrome is less well defined than the other syndromes. Its stages may be compressed due to the relatively high radiation dose at which

Table 5
Grading system for cutaneous response[a]

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
Erythema	Minimal and transient	Moderate, < 10% BSA	Marked; 10–40% BSA	Severe; > 40% BSA
Sensation/itching	Pruritus	Slight and intermittent pain	Moderate and persistent pain	Severe and persistent pain
Swelling/edema	Present; 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/necrosis	Epidermal only	Dermal	Subcutaneous	Muscle/bone involvement
Hair loss	Thinning, not striking	Patchy, visible	Complete and reversible	Complete and irreversible
Onycholysis	Absent	Partial	Partial	Complete

[a]Modified from Fliedner et al. (2001).

Table 6
Grading system for neurovascular and gastrointestinal responses[a]

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
Neurovascular system				
Nausea	Mild	Moderate	Intense	Excruciating
Vomiting	Occasional, 1/day	Intermittent, 2–5/day	Persistent, 6–10/days	Refractory > 10/days
Anorexia	Able to eat	Intake decreased	No intake	Parenteral nutrition
Fatigue syndrome	Able to work	Impaired work	Assistance for ADLs	No ADLs
Fever	< 38 °C	38–40 °C	> 40 °C < 24 h	> 40 °C > 24 h
Headache	Minimal	Moderate	Intense	Excruciating
Hypotension	HR > 100/BP > 100/170	BP < 100/70	BP < 90/60; transient	BP < 80/uncertain; persistent
Neurological deficits	Barely detectable	Easily detectable	Prominent neurological	Life threatening, LOC
Cognitive deficits	Minor loss	Moderate loss	Major impairment	Complete impairment
Gastrointestinal system				
Diarrhea				
Frequency	2–3 stools/day	4–6 stools/day	7–9 stools/day	> 10 stools/day
Consistency	Bulky	Loose	Loose	Watery
Bleeding	Occult	Intermittent	Persistent	Persistent with large amount
Abdominal cramps/pain	Minimal	Tolerable	Intense	Excruciating

[a]Modified from Fliedner et al. (2001).

Table 7
Grading system for hematopoietic response[a]

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
Lymphocyte changes	$\geqslant 1.5 \times 10^9$/l	$1–1.5 \times 10^9$/l	$0.5–1 \times 10^9$/l	$< 0.5 \times 10^9$/l
Granulocyte changes	$\geqslant 2 \times 10^9$/l	$1–2 \times 10^9$/l	$0.5–1 \times 10^9$/l	$< 0.5 \times 10^9$/l or initial granulocytosis
Thrombocyte changes	$\geqslant 100 \times 10^9$/l	$50–100 \times 10^9$/l	$20–50 \times 10^9$/l	$< 20 \times 10^9$/l
Blood loss	Petechiae; easy bruising; normal Hb	Mild blood loss with < 10% decrease in Hb	Gross blood loss with 10–20% decrease in Hb	Spontaneous bleeding or blood loss with > 20% decrease in Hb

[a]Modified from Fliedner et al. (2001).

this syndrome typically appears (see Fig. 1). Individuals receiving doses in excess of 20–30 Gy present with fever, hypotension and major impairment of cognitive function. Table 6 assigns degrees of toxicity to the neurovascular system based upon these neurological and cognitive deficits and other symptoms, including nausea and vomiting. The rapid course of this syndrome is characterized by disorientation and confusion during the prodromal phase, and initial presentation may include disorders of balance and seizure activity. Physical examination may reveal papilledema, ataxia, reduced or absent deep tendon reflexes and absent corneal reflexes. The latent period may last only a few hours and is followed by fever, respiratory distress, diarrhea and cardiovascular collapse. Death often occurs within a few days.

Cutaneous syndrome: The cutaneous syndrome may develop within 1–2 days but may take years before becoming fully manifest. Early lesions include erythema and edema of the skin. Advanced lesions include blisters, bullae (with or without hemorrhage), dry or moist desquamation, ulceration and onycholysis. Epilation may occur at 10–20 days after a single localized dose of 3–4 Gy; but, the presence or absence of skin epilation and other reactions can be misleading since are very depen-

Table 8
Biodosimetry based on acute photon-equivalent exposures[a]

Dose estimate	Time to onset of vomiting		Absolute lymphocyte count ($\times 10^9$/l)[b] (day)						Lymphocyte depletion rate[c]	Number of dicentrics[d]	
Gy	%[e]	Time (h)	0.5	1	2	4	6	8	Rate constant	Per 50 cells	Per 1000 cells
0	–	–	**2.45**	**2.45**	**2.45**	**2.45**	**2.45**	**2.45**	–	0.05–0.1	1–2
1	19		**2.30**	**2.16**	**1.90**	**1.48**	1.15	0.89	0.126	4	88
2	35	4.63	**2.16**	**1.90**	**1.48**	0.89	0.54	0.33	0.252	12	234
3	54	2.62	**2.03**	**1.68**	1.15	0.54	0.25	0.12	0.378	22	439
4	72	1.74	**1.90**	**1.48**	0.89	0.33	0.12	0.044	0.504	35	703
5	86	1.27	**1.79**	1.31	0.69	0.20	0.06	0.020	0.630	51	1024
6	94	0.99	**1.68**	1.15	0.54	0.12	0.03	0.006	0.756		
7	98	0.79	**1.58**	1.01	0.42	0.072	0.012	0.002	0.881		
8	99	0.66	**1.48**	0.89	0.33	0.044	0.006	<0.001	1.01		
9	100	0.56	1.39	0.79	0.25	0.030	0.003	<0.001	1.13		
10	100	0.48	1.31	0.70	0.20	0.020	0.001	<0.001	1.26		

Depicted above are the three most useful elements of biodosimetry. Dose range is based on acute photon-equivalent exposures. The first column indicates the percent of people who vomit, based on dose received and time to onset. The middle section depicts the time frame for development of lymphopenia. Two or more determinations of blood lymphocyte counts are made to predict a rate constant which is used to estimate exposure dose. The final column represents the current "gold standard" which requires several days before results are known. Colony stimulating factor (CSF) therapy should be initiated when onset of vomiting or lymphocyte depletion kinetics suggests a dose for which treatment is recommended. Therapy may be discontinued if results from chromosome dicentrics analysis indicate a lower estimate of whole-body dose.

[a] Waselenko et al. (2004).
[b] Normal range: 1.4–3.5 $\times 10^9$/l. Numbers in bold fall within this range.
[c] The lymphocyte depletion rate is based on the model $Lt = 2.45 \times 10^9/l \times e - k(D)t$ where Lt equals the lymphocyte count ($\times 10^9$/l), 2.45×10^9/l equals a constant representing the consensus mean lymphocyte count in the general population, k equals the lymphocyte depletion rate constant for a specific acute photon dose, and t equals the time after exposure (days).
[d] Number of dicentric chromosomes in human peripheral blood lymphocytes.
[e] Cumulative percentage of victims with vomiting.

dent on the radiation source energy and can be somewhat unpredictable if the energy is unknown or poorly defined. Table 5 assigns degrees of toxicity to the cutaneous system based upon these findings and other symptoms, including pruritis and hair loss. Chronic skin changes, including fibrosis and scarring, chronic ulcers and lentigo may persist for many years.

Appendix I. Dose estimation based on location history

There are two general categories for radiation dose consideration from unintentional exposures of substantial health interest to members of the general public. The first of these is internal exposure and typically would come from inhaled radioactivity originating from aerosolized sources. The second is from external exposure due to either radiological exposure devices or from dispersed sources. Although combinations of these are also possible, dosimetry for each exposure pathway would not be substantially affected as they would generally be independently addressed. The one common requirement for initial absorbed dose estimation in either scenario is that of obtaining a full location history of individuals who could have been exposed. Issues associated with these types of location-based dose estimations are presented separately below. The unlikely event of injection of radioactivity (through wounds) would be handled on a case by case basis as any wound arising from an RDD would already be assumed to be contaminated and handled accordingly.

Aerosolized source terms: Airborne radioactivity (not to include radon and its progeny) of potential health concern often assumes a mechanism capable of aerosolization of radioactive material. Alternatively, the material may already be in an easily dispersible form such as granular salts or powders. A worst case particle size should initially be assumed to ensure adequate protections are employed (e.g. shelter in place or evacuation). As measurements become available on particle size distributions, adjustments can be made to the dose calculations to the extent warranted by the measurements. Consideration should be given to possible geographic variations in particle size distributions if aerosol measurements are not comprehensively evaluated to exclude or actually quantify this potential. In principle, one would expect the larger particles to plate out closer to the source for an RDD.

The location history information along with subsequent graphical information system (GIS) generated source term distributions can then be used to generate initial dose estimates based on an integration of position dependent dose rate over time for each individual. This would be done by assessment scientists as they become available in the response effort as multiple variables will likely need to be simultaneously considered.

If initial dose estimates are based on time and motion estimates of individuals exposed to the plume, final dose estimation for individuals should be based on biodosimetry. If the uncertainties in initial absorbed dose based on uptake estimates are within an order of magnitude of dose limits of interest,

serious consideration should be given to recommending these individuals be quickly assessed by direct (e.g. whole-body counting) or indirect bioassay to the extent practical. These measurements will be more accurate than absorbed dose estimates obtained from either location histories or air concentration measurements.

External exposure source terms: As with the initial response to aerosolized source terms, full location histories of individuals will need to be obtained to the extent practical for all potentially exposed individuals. These preliminary absorbed dose estimates will almost certainly be the first estimates available until measurements of the source term have been made and appropriately analyzed.

As external source terms could be comprised of either an occult source or large activity pieces of radioactive material not aerosolized in an explosive dispersion event, large gradients in dose rates could be components of individual dose histories. These could include items such as brachytherapy seeds (e.g. Juarez incident) or other lost source events (e.g. Goiana). If the source term is a largely homogenous distribution of activity such as would be expected from ground deposition from a large dispersed radioactive plume, detailed location history would be less critical than for heterogeneous distributions including point sources as the uncertainty in the latter would by nature be larger than the former.

In the event of dispersed activity, mapping of activities would need to be conducted as rapidly as safely possible to ensure accurate dose rate distributions are obtained. This can be done using aerial measurements if the distribution is not characteristically heterogeneous. Heterogeneous features such as multiple point sources in relatively close proximity (within a few hundred feet) should be mapped out with ground-based methods in order to obtain sufficient detail of dose rates for dose reconstruction estimations if not at least bounding dose estimates.

All activity and dose rate mapping should be done in ways readily amenable to standard GIS capabilities to ensure accurate information is communicated in the final products. Any inaccuracy of the predicted and measured values on maps will not be readily understood by the decision makers and will erode their confidence in the response teams' efforts as a whole.

Ingestion source terms: Unless food is eaten within the first few days after a known release, food crops will be very quickly controlled by local authorities following a large release of airborne radioactive particulate. Within the first few days of the release, the total footprint would be quantified so that accurate determination of contaminated food locations would be well characterized. As this food would have to have been very recently harvested after the event for it not to have been controlled, it would not be difficult to compare the food source location with mapped radioactivity to determine if an ingestion dose were credible for any potential follow-up activities.

Mixed internal and external source terms: Although airborne radioactivity will contribute to an external dose contribution, mixed source contributions are also possible during the initial plume phase if an individual were in the immediate vicinity. Ideally, the smoke from an incendiary device would to some extent transport with the radioactivity giving impetus for individuals to move themselves away from the radioactivity (due to their desire to get out of the smoke). If mixed source terms were identified from a person's location history, these should be dealt with independently during the generation of initial dose estimates.

Appendix J. Summary of prior uses of biodosimetry

Biodosimetry applications in radiation accidents: Prior to 1970, physicians tasked with the medical management of acute radiation injury had to rely on the development of signs and symptoms of radiation injury as previously described. However, since that time the DA has been extensively developed and harmonized to international standards (IAEA, 2001). Table 9 lists

Table 9
Selected use of acute-phase cytogenetic biodosimetry in radiation accidents[a]

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

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

Table 10
Acute-phase estimates of dose (Gy) after the Tokaimura incident (1999)

Method	Patient O	Patient S	Patient Y
Na-24 blood (*n* only)	9.1	5.0	1.2
Rings + dicentrics	21	6.6	2.8
PCC (*Y* equivalent)	> 20	7.8	2.6
Na-24 WBC			1.6
Lymphocyte kinetics	> 10	6–10	1–4.5
Survival	Death 82 days post-exposure	Death 210 days post-exposure	Alive

Table 11
Selected use of acute-phase EPR in radiation accidents

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

selected recent radiation accidents where dicentric and PCC biodosimetry have played an important role in acute or near phase management. Examples of some important recent applications are summarized below.

Results of the cytogenetic studies of the 1986 Chernobyl accident have been summarized (Sevan'kaev, 2000). Chromosomal aberration dosimetry was used in the acute phase of the Chernobyl accident as a method of dose assessment. A good correlation was observed between doses calculated based on chromosomal aberrations (dicentrics) and the severity of acute radiation syndrome observed clinically.

Soon thereafter, a radiation accident involving a ^{137}Cs therapy source occurred in Goiânia (Brazil), in which more than 50 individuals were exposed to moderate to high doses (0.2–7 Gy) of gamma radiation. A cytogenetic technique (i.e. frequencies of dicentrics and rings in peripheral lymphocytes) was employed (Ramalho and Nascimento, 1991) in the acute phase to estimate absorbed doses from this accident. They described a follow-up study in which an exponential decline in the dicentric lymphocyte frequency was observed. Using chromosome-specific library probes for chromosomes 1, 2, 8 and 19, Ramalho and others studied the frequencies of chromosomal translocations and deletions and the incidence of aneuploidy in the lymphocytes of exposed individuals from this accident. In some individuals there was a significant increase in the frequency of translocations and aneuploidy.

The radiation accident at Tokaimura in 1999 is a well-studied uranium criticality accident that is important because it was witnessed and multi-parameter triage techniques were employed in the acute-phase medical management. The frequency of chromosome aberrations in circulating lymphocytes was found to be a reliable indicator of the absorbed dose.

Table 10 presents a comparison between various acute-phase techniques for this criticality incident. All table entries represent data contemporaneous with acute patient care, and not from a retrospective analysis. Lymphocyte kinetics and the time to emesis were evaluated in real time, and the results of chromosome biodosimetry were available quickly enough to impact clinical decisions when taken in the context of evolving symptom complexes. In general, there is good agreement on dose prediction when these techniques were employed early in the incident. The proceedings of a general symposium including an improved retrospective analysis of the source term, power spectra, and medical treatment are available (Tsujii and Akashi, 2000).

In some accident cases in which a strong lymphopenia was detected (e.g. Istanbul accident in which 10 people from two families were involved), chromosome-painting techniques were found to be more accurate in the evaluation of dose than dicentrics, due to better stability of translocations detected by FISH (IAEA, 2000).

Traditionally, EPR dosimetry has been used primarily in the retrospective analysis of radiation accidents and has been quite valuable in this regard. It has been particularly helpful where an amputation has occurred and where bone fragments have been available from a site of severe local irradiation. These samples have often been the result of a surgical amputation days to weeks post-accident. Table 11 presents selected cases where EPR has been useful in radiation accidents.

In the last 10 years, EPR has increasingly been considered as a biodosimetric tool for the acute-phase analysis of radiation incidents. In the US, various reports are available (Schauer et al., 1993, 1994, 1996; Romanyukha et al., 2005) from accelerator accidents and from various types of severe, acute local injury. In addition, the 1991 San Salvador accident involving a ^{60}Co source posed significant non-uniform injury, particularly to the toes and femur. A detailed EPR analysis of femur available from that accident has been presented by Desrosiers (1991). Recent analysis of the multi-casualty radiation accident in Lilo, Georgia has used EPR techniques in acute-phase analysis and this work has recently been reviewed (Clairand et al., 2006).

In the radiation accident in Tammiku, Estonia (1994) a large ^{137}Cs was stolen from a poorly guarded radioactive waste depository and taken by three brothers to their home. Various members of the family were exposed to this source, chronically and in a non-uniform manner. In particular, the most severely injured patient received 1830 Gy to the femur and thigh, and approximately 4 Gy acute whole-body dose. He soon died of multi-organ failure. Other members of his family received 0–4 Gy whole-body dose over 28 days and up to 20–30 Gy acute local dose to the hands. This case is interesting because various acute-phase modalities were employed in dose reconstruction: (1) chromosome aberration dicentric analysis, (2) Glycophorin A somatic mutation assays, (3) TL dosimetry, (4) optically stimulated luminescence (OSL), (5) EPR dosimetry, (6) chemiluminescence, and (7) Monte Carlo modeling of spatial effects. The use of EPR in this event was a valuable adjunct to clinical analysis of the ARS and of acute local injury.

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