HHS Public Access

Author manuscript

Radiat Environ Biophys. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Radiat Environ Biophys. 2014 May ; 53(2): 221–232. doi:10.1007/s00411-014-0522-0.

Overview of the principles and practice of biodosimetry

Harold M. Swartz, **Benjamin B. Williams**, and **Ann Barry Flood**

EPR Center for the Study of Viable Systems, Geisel School of Medicine at Dartmouth, Hanover, NH, USA

Abstract

The principle of biodosimetry is to utilize changes induced in the individual by ionizing radiation to estimate the dose and, if possible, to predict or reflect the clinically relevant response, i.e., the biological consequences of the dose. Ideally, the changes should be specific for ionizing radiation, and the response should be unaffected by prior medical or physiological variations among subjects, including changes that might be caused by the stress and trauma from a radiation event. There are two basic types of biodosimetry with different and often complementary characteristics: those based on changes in biological parameters such as gene activation or chromosomal abnormalities and those based on physical changes in tissues (detected by techniques such as EPR). In this paper, we consider the applicability of the various techniques for different scenarios: small- and large-scale exposures to levels of radiation that could lead to the acute radiation syndrome and exposures with lower doses that do not need immediate care, but should be followed for evidence of long-term consequences. The development of biodosimetry has been especially stimulated by the needs after a large-scale event where it is essential to have a means to identify those individuals who would benefit from being brought into the medical care system. Analyses of the conventional methods officially recommended for responding to such events indicate that these methods are unlikely to achieve the results needed for timely triage of thousands of victims. Emerging biodosimetric methods can fill this critically important gap.

Keywords

Unplanned exposures; Biodosimetry; Radiation; Ionizing radiation; Terrorism

Requirements for dosimetry for various types of radiation events

This paper attempts to provide a systematic overview of the principles and practice of biodosimetry. We consider three types of scenarios:

1. A *large-scale radiation event* in which many are potentially affected and therefore early triage is the most pressing need. Planners and researchers use differing magnitudes to define large-scale events, ranging from as few as 100 people to a million or more.

Correspondence to: Harold M. Swartz.

Disclaimer: HMS and ABF are co-owners of Clin-EPR, LLC, which manufactures clinical EPR instruments for investigational use only.

2. A *small-scale radiation event* such that it is practical to enter all potentially affected individuals into the healthcare system for initial evaluation and subsequent care. Most of our experience with biodosimetry comes from radiation accidents involving very few, up to a few dozen, people.

3. An exposure where the focus is only on long-term effects. In this paper, this primarily includes identifying people whose exposure was potentially high enough to warrant long-term follow-up but who did not warrant immediate triage for acute care. Survivors identified as needing immediate care would also be monitored long term.

We especially focus on the needs following a large-scale radiation event such as a major nuclear power plant malfunction or terrorism involving release of radioactive material and/or radiation exposure, because this will be the situation where there will be the most urgent need for biodosimetry for rapid decision making. In a large-scale event involving hundreds of thousands of people, the medical system will be incapable of coping with all potentially exposed individuals. In some instances, such as the nuclear power plant accident that occurred in Japan in 2011, the number of life-threatening exposures may be very small, but the need for large-scale measurements may still exist because of a lack of trust in reassurances from authorities. If an event does involve significant exposures, such as a 10-kiloton nuclear weapon detonated in a large urban area, there may be more than a million people who would be appropriate to be evaluated for exposure (Buddemeier and Dillion 2009; Gougelet et al. 2010; Grace et al. 2010; Waselenko et al. 2004). Then it will be essential to have an effective initial triage, so limited resources can be focused on those who are most likely to have received a dose high enough to potentially benefit from treatment for acute radiation syndrome (ARS), by distinguishing them from those who would not. Preferably, such information would be based on knowing the dose for each individual. However, the consensus for triaging very large populations based on dose is to set a reasonable cutoff of dose received, below which treatment is not expected to impact survival rates and above which treatment is necessary to improve survival rates. This cutoff is generally set at 2 gray (Gy). The threshold could plausibly be set higher, e.g., 3 Gy if the numbers of affected individuals were beyond the capabilities of the medical system (DiCarlo et al. 2011; Grace et al. 2010; Rea et al. 2010; Flood et al. 2011). There are circumstances, including combined injury, when the threshold could be set lower, e.g., 1 Gy. In any case, the likely uncertainty allowed for initial triage is related to the precision appropriate for clinical decision making, such as ±0.5 Gy around the threshold.

Following an initial screening to identify individuals who need immediate medical attention, a second stage, with more refined assessments of the absorbed dose, likely coupled with information about the patient's biological reactions to radiation and other information indicative of exposure, can help direct effective clinical management (Coleman et al. 2009; Flood et al. 2011, 2012; Grace et al. 2010).

The requirements for a small-scale event are quite different in many important ways. If all potentially affected individuals can be entered into the healthcare system for diagnosis, monitoring, and care, then the emphasis changes to understanding the biological implications of the injury for the individual, not the dose per se. There is much less need for

rapid estimates of the dose, particularly for whole-body exposures (which is the focus of this paper), and the goal changes to providing information for treatment decisions. In this case, techniques such as those based on changes in white cells may be very effective as well as biodosimetry techniques that reflect the implications for the individual.

The requirements for understanding long-term effects such as cancer and deleterious mutations are different than for the acute effects. The doses involved are likely to be much lower. The need changes to techniques that can provide estimates of dose many months or years after the event.

It should be noted that this analysis does not include biodosimetry and related techniques for internal exposures from radionuclides. Those need to be addressed by very different approaches that involve detection of the radioactivity from the radionuclides, and the calculation of resultant doses is very complex and uses quite different techniques. Similar considerations apply to radioactivity induced by neutrons.

Potential means to assess dose for a radiation event

Before turning to the discussion of biodosimetry for various types of events, it is useful to outline the other methods currently available to assess dose.

Conventional physical dosimetry

Dose estimates based on conventional physical dosimetry can be based on *direct measurements* of radiation via physical dosimeters or environmental monitoring devices for radiation or on *indirect measurements* by calculating likely dose based on known characteristics of the event and the individual's distance from the source and the duration of the exposure. These methods, while useful for some scenarios such as overexposures from small-scale accidents, are very unlikely to be adequate for prompt assessment of individual exposures in large scale. Conventional physical dosimeters require that they be worn routinely and/or prepositioned, neither of which is likely to be practical or effective for large events. Also, when indirect methods, based on calculations of the dose distribution from the characteristics of the event, are used to assess individuals' exposures, serious problems arise when applied to large-scale populations. Problems include the considerable time needed to reconstruct and calculate the dose distribution, along with difficulty of relating such results to individuals due to uncertainties about their location at the time of the event and their duration of exposure. Moreover, medical triage of large populations based on indirect methods may not be very acceptable to individuals because of distrust of these types of "statistical" estimations about a group and/or about the reliability of the authorities.

Alternative physical dosimeters

Alternative modes of physical dosimeters have been used for small incidents, such as optically stimulated luminescence (OSL)- or electron paramagnetic resonance (EPR)- based studies of objects in the environment. These also have been investigated for use for large-scale events, including techniques such as deliberately embedding radiation-sensitive materials in objects commonly carried by individuals (e.g., credit cards, cell phones) or researching the dosimetric properties of their current construction (e.g., plastic buttons, glass

covers on watches; Bassinet et al. 2010a, 2010b; Sholom and Chumak 2010; Trompier et al. 2010, 2011; Yordanov et al. 2002). Others have suggested identifying potential adventitious physical dosimeters, such as estimating dose due to radiation-induced changes in nearby physical structures (such as brick buildings; cf. Buddemeier 2010). However, they also have some disadvantages that render them impractical for large events and initial triage, including whether they are likely to be available and usable to estimate a personal dose, whether the material being queried is consistently manufactured so as to have a known native signal or a uniform response to radiation. For example, Trompier et al. (2013) reported that cell phones were constructed from several types of glass; moreover, 14 % of phones they tested used glass that did not respond to radiation, and the majority of phones used a glass that exhibited a signal prior to radiation. Sholom et al. (2011) used OSL to measure business cards, plastic buttons, and nails and found that samples often exhibited strong signals prior to radiation and showed rapid fading of the signal after a few hours of storage in ordinary laboratory lighting.

It should be noted that physically based biodosimetric techniques, in contrast, assess dose by directly measuring the physical changes in tissues of individuals such as their bone, teeth, hair or nails and therefore are quite distinct from the alternative physical dosimeters because of their nature and that they always are in a known place in the subject.

Individual dosimetry based on clinical signs and symptoms

Because of these likely problems with estimating dose using conventional physical dosimeters or calculations of exposures, current advice as offered in various official documents, Web sites, and consensus papers emphasizes methods to measure radiation effects by directly observing each individual’s response (Alexander et al. 2007; Buddemeier and Dillon 2009; Buddemeier 2010; CDC 2006; Grace et al. 2010; González 2007; US Department of Health and Human Services 2013). This has been useful for small events but does not readily extend to large-scale events. To triage large numbers of people and the likely scenario of infrastructure problems during the first few days following a major disaster, an objective analysis of the current methods to assess dose to carry out initial triage following a large event indicates that effective triage is not likely to be achieved using what is currently available and recommended (Flood et al. 2011, 2012; Nicolalde et al. 2012; Swartz et al. 2010, 2011).

The methods that conventionally are recommended for assessment at the level of the individual are clinical signs and symptoms, and assays based on changes in white cells. There are, however, no clinical signs and symptoms that are characteristic for ionizing radiation that occur promptly enough to facilitate triage, with the possible exception of time to emesis. The situation with time to emesis is complex, however. This is a “test” that can be carried out by nonexperts in the field, and if it occurs, it happens within hours to days. Ronald Goans and associates have assembled a moderate-sized database (107 individuals) principally comprised of people exposed at Chernobyl but also of about 20 individuals from the REAC/TS database, in which they have plotted the relationship between time to emesis and estimated dose (Goans 2002). While in their publication, they clearly indicate the potential limitations of these data [see also Demidenko et al. 2009 and the radiation

emergency medical management Web site (US Dept. Health and Human Services 2013; Flood et al. 2013) for further elaboration on these potential limitations], there has been a tendency to advocate the use of time to emesis well beyond its statistical validity and to ignore other shortcomings in these data. For example, the published data have an uncertainty of several gray in the prediction of dose from time to emesis (Demidenko et al. 2009). In addition, the published relationship does not include individuals who did not vomit. While Goans and coworkers have provided some data on this aspect from the early whole-body irradiation therapy program at Oak Ridge (Goans et al. 2001), there remain several problems in generalizing their results to other events: (1) The populations involved in the accidents are not representative of the population that would be exposed in a large-scale incident. For example, the people exposed at Chernobyl to high doses of radiation also suffered from complex injuries including extensive skin damage, total body irradiation, extreme stress including overheating and had a very different demographic profile (i.e., they were mostly young and male) than the general population. (2) The use of the existing data does not take into account the very real potential, especially in a large-scale event, of psychosocial origins of emesis (including fear and contagion of witnessing others vomiting). And (3) the use of this endpoint potentially could be further confounded by the use of emetics by terrorists to cause fear and misidentification of radiation levels by adding emetics to a small device such as a radiation dispersal device (dirty bomb).

White cell-based biodosimetry

There are five types of commonly considered approaches: dicentric chromosome analysis (DCA), premature chromosome condensation, cytokinesis block micronuclei (CBMN), fluorescence in situ hybridization (FISH), and lymphocyte depletion rate (LDR) (Fenech 2011; Ainsbury et al. 2011). Some of these have been applied successfully for small-scale incidents and/or for epidemiological assessment of large-scale events. But their suitability for large-scale use in the field seems very challenging, because the capacity for carrying out the assays would be overwhelmed by events involving even a few thousand individuals (Flood et al. 2011; Gougelet et al. 2010; Parker and Parker 2007; Wojcik et al. 2010; Maznyk et al. 2012). All of these share the need for removal of blood samples into special containers (but this can be done in some cases with a simple pinprick). More importantly, currently they all require processing by expert personnel. There also are varying degrees of special equipment needed. All five of the approaches might be challenged by the needs for throughput. The FISH and DCA assays require at least 4–5 days of processing until results will be available. The LDR assay requires obtaining several samples from each victim over time. While several authors have proposed modifying the conventional DCA under disaster circumstances requiring triage by scoring fewer metaphase spreads (Lloyd et al. 2000; Vaurijoux et al. 2009; Romm et al. 2011; Beinke et al. 2013), DCA still requires experts to analyze and so entails only modest increases in throughput. There have been some significant efforts to improve throughput for some assays, such as by automating the sample flow for CBMN (Garty et al. 2010; Turner et al. 2011) or by simplifying the culturing and scoring techniques for CBMN (McNamee et al. 2009; Fenech et al. 2013; Romm et al. 2013). Horn and Rothkamm (2011) suggested extending the number of days that Gamma-H2AX could be valid for dosimetry by combining protein bio-markers and examining the temporal patterns. Rothkamm et al. (2013) compared four laboratories' scoring after 2 and

24 h following irradiation and varying numbers of scored cells (20–50 cells) and found evidence that low and high doses could be discriminated with sufficient accuracy despite some inter-laboratory differences.

These developments, while promising, tend to require modifications in the methods that result in lowering the accuracy of the method, i.e., reducing the standards needed for “triage mode” decisions. Moreover, they tend to implicitly confine the capacity to respond to relatively small “mass events.” For example, Pinto et al. (2010) in their review suggest that the maximum number of people to be assessed for purposes or triage-mode dosimetry ranges from tens to hundreds of individuals. Two surveys assessed the current capacity of laboratories in Europe (Wojcik et al. 2010) and worldwide (Maznyk et al. 2012) to perform biologically based biodosimetry including DCA, FISH, CBMN, and gamma-H2AX. Their evaluations also suggest that—despite current attempts to build networks of laboratories, simplify and automate the methods, and reduce the requirements for triage-level sensitivity and specificity of the results—a maximum number of victims between 100 and 3,000 could be assessed in a timely way to support triage using these methods.

The nature of biodosimetry

Having briefly reviewed the basic types of other dosimetry methods available, we turn to the underlying theory and various purposes of biodosimetry. For the purposes of this discussion, we now consider the emerging methods of biodosimetry that have the potential for significantly advancing the ability to assess the risk to individuals. The principle underlying these biodosimetric techniques is to utilize changes in the tissues of the individual induced by ionizing radiation as a quantitative measure of the amount of radiation energy that was absorbed (Swartz et al. 2010; Flood et al. 2011). There are potentially many parameters that could be measured (Brengues et al. 2010; Coy et al. 2011; Flood et al. 2011; Gougelet et al. 2010; Ossetrova et al. 2010; Rana et al. 2010), and some/most of them were already addressed above. There are several different potential approaches for biodosimetry: (1) *measure the radiation-induced changes directly* when they occur in amounts that are not normally present even under pathological conditions, e.g., physical changes such as stable free radicals (Fattibene and Callens 2010) or products such as volatile gases (Phillips et al. 2013), (2) *measure the biological response to the damage* cause by the radiation, e.g., by up-regulation of genes (genomics) (Paul and Amundson 2008) or protein products (proteomics) (Marchetti et al. 2006), and/or (3) *measure the biologically modified products* from the radiation (metabolomics) (Ainsbury et al. 2011; Coy et al. 2011).

Note: In the discussion, we have not considered approaches that might plausibly also be considered biodosimetry, based on damage to white blood cells (WBCs) or clinical symptoms which do reflect parameters within the individual.

Specific purposes of biodosimetry

There are a number of different uses for biodosimetry, which require different features for optimal utility. The potential applications include:

1. Determining who needs to go into the healthcare system initially.

2. Determining more definitively who needs to go into the healthcare system after the initial triage.
3. Guiding treatment by dose estimates.
4. Guiding treatment by estimates of homogeneity of the exposures
5. Guiding treatment specific for damage to particular organs such as the lung.
6. Monitoring the effectiveness of therapy.
7. Estimating long-term risks/consequences.

Desired properties of any biodosimetry technique

An ideal biodosimetric technique would meet several specific criteria. While it is unlikely that a single technique would meet all of these criteria, they may be achieved by a combination of approaches. The needs for these characteristics also will vary with the type of event, so there can be no “gold standard” that addresses all of the purposes noted above. Key criteria include the capacity for the parameter to:

1. Be specific to ionizing radiation;
2. Have well-known effects by type of radiation and by dose rate;
3. Be unaffected by prior health status or concurrent perturbations such as wounds or stress;
4. Have a well-characterized dose–response that is either unaffected by individual variations or known for the type of individual being measured (e.g., based on gender);
5. Reflect biological implications to the individual;
6. Have a constant or well-known response over the full period of relevant times;
7. Allow to provide results quickly;
8. Allow to be accomplished for the population at risk within the appropriate time frame; and
9. Be suitable for the expertise that is likely to be available for the circumstances in which they will be used.

Biologically based biodosimetry—Biodosimetric methods that use biological responses to ionizing radiation have the potential to provide information that is more directly related to the clinical consequences of the radiation for a particular individual. Since it is well established that the biological effects of the same amount of a damaging event will vary among individuals, individualized determinations of the effects can be quite important for medical decision making, because treatment is likely to be most effective when based on the individual’s specific responses to radiation rather than simply “treating the dose.” While some biologically based assays involve the detection of unusual molecules, the vast majority of the biologically based biodosimetric techniques are based on the principle of estimating the dose by assessing the magnitude of the responses of cells and tissues to any damaging

events. In general, these responses involve existing systems whose function is to respond to physical injury or pathophysiological processes such as disease. There are many such systems, usually involving complex interactions, which therefore provide a rich array of changes to assay for the purpose of dosimetry. One such type of biologically based assay measures the responses themselves. Genomics, for example, estimates dose by assaying the activation of genes that were up or down-regulated as a part of the damage-response pathways. Another type of biological assay detects the presence of products produced by the pathways to carry out the responses to radiation damage, such as proteins (proteomics) or messenger ribonucleic acid (mRNA). Some assays detect the presence of small molecules that are produced directly by the radiation or, more typically, the metabolic products resulting from the damaged molecules (metabolomics). Alternatively, assays can assess indicators produced during the process of repair, especially those related to deoxyribonucleic acid (DNA) such as 8-hydroxyguanine or fragments of DNA.

All of these types of assays share common features that lead to potential advantages as well as potential challenges for their use as biodosimeters. There are two very important potential advantages:

1. They have the potential for reflecting the biological consequences of the radiation dose in a particular individual. As described above, this type of information is more valuable for clinical decision making than is the dose, because individuals vary in their responses and, consequently, treatment should take into account the individual's reaction to injury. For example, individuals may respond to the same dose with quite different degrees of suppression of the bone marrow, which in turn should influence decisions about whether or when to consider bone marrow transplant.
2. They use the biological response as a type of amplifier. This amplification of the response leads to the potential to be very sensitive, thereby allowing more accurate and specific dose estimates.

There are, however, also several potential limitations of this type of biodosimetry that curtail its applicability as a technique, especially for initial triage in large-scale events:

1. Because these techniques usually are based on biological pathways for responding to injury, they are not specific to ionizing radiation and thus cannot uniquely corroborate whether the response was due to injury from ionizing radiation.
2. This in turn complicates any interpretation about radiation exposure if the person was exposed to any concomitant injuries such as stress, burns, and physical trauma (which are likely to occur in the postulated event) or even to recent and unrelated injury from disease or its treatment.
3. Even without other injury, the fundamental temporal pattern of any damage-response pathway results in complex temporal changes that seriously complicate the interpretation of the measurement and limit the time during which the assay can be validly sampled. The pattern usually begins with an induction period between the occurrence of the damaging event and the up-regulation or down-

regulation of the response element, resulting in a delay in being able to observe the product. This period is followed by a period of active response, during which the level of the response and the amount of the products of the response are rapidly changing. In many cases, this is followed by a plateau period, when there is a constant amount of the product. Finally, the system returns toward and finally reaches its original baseline level. Since these temporal changes impact the level of the response that is present, the timing of when the sample is collected is important to take into account in assessing dose.

4. The baseline level of the pathway and the product will be affected by physiological variations among individuals and especially by effects from *preexisting* conditions. Information about the baseline level, even if knowable under some circumstances, is unlikely to be known for an individual in a major radiation event.

5. The timing and extent of changes in the pathway and the product also will be affected by the same factors that affect the baseline level.

These factors taken together tend to limit the feasibility of using biologically based assays for initial triage of large-scale events, which are likely to use temporary facilities with initial staffing by response teams located nearby to the event. However, if it is possible to elicit information about prior medical conditions and concurrent injuries, the utility of these assays would be enhanced. Their value also increases if these assays can be repeated over time, thereby allowing determination of temporal trends. Importantly, because they also have the potential for indicating the biological consequences of the radiation dose, their results can guide more specific treatment decisions.

Thus, to take advantage of their strengths and minimize their limitations, the biologically based biodosimetry methods are arguably better suited if used to care for people after they have been initially triaged for care, using methods more suitable for initial triage, and/or used for small events where all potentially affected individuals can be placed into the healthcare system. The principal advantage of using these techniques in secondary stages of triage for large-scale events or in small events is because it is more feasible that these stages will take place in an organized medical facility housing the subjects and the expertise needed to carry out the techniques. For example, such facilities would minimize or eliminate the problems associated with requirements to transport samples to a specialized offsite laboratory for analysis and be able to report results to appropriate medical decision makers who are to take advantage of their strengths and minimize their limitations.

Physically based biodosimetry

Physically based biodosimetric techniques assess dose by directly measuring the physical changes in a person’s tissues. When the products of the radiation-induced changes in tissues are unique, or at least occur with a much greater frequency or magnitude than normal, then the changes measured are likely to be very specific to ionizing radiation. The two most frequently used physically based biodosimetric techniques are EPR (Fattibene and Callens 2010) and OSL (DeWitt et al. 2010). When used for biodosimetry, EPR measures the amount of free radicals induced in hydroxyapatite (present in tooth enamel and bone) or

keratin (in nails) from exposure to ionizing radiation. Biodosimetry using OSL measures the response in tissues such as teeth to absorbing energy from ionizing radiation.

Unfortunately, the use of OSL as a physically based biodosimeter is critically limited by the fact that ambient light rapidly degrades the signals observed with OSL, thus requiring the person (or sample) to be kept in the dark following exposure until OSL measurements can be taken (McKeever et al. 1997; Yukihara et al. 2007; Sholom et al. 2011). This limitation, until resolved, renders this approach impractical for most radiation incidents, including triage.

EPR biodosimetry methods, in contrast, that rely on bone or enamel biopsy or extracted teeth have been used successfully for long-term retrospective analysis or corroboration of dose in small accidents or major events such as Chernobyl (see review in Fattibene and Callens 2010). However, these techniques are severely limited in their usefulness for triage by their invasive process, inducement of permanent injury, and their need for analysis by specialized facilities and expertise.

EPR techniques that can make in vivo measurements (such as on teeth or nails) or which are minimally invasive (such as using clipped nails) have been shown to be feasible for obtaining data under the postulated conditions (Swartz et al. 2007; Williams et al. 2011; He et al. 2014). These are currently being extensively developed at Dart-mouth via a NIH Center for Medical Countermeasures Against Radiation (CMCR) dedicated to EPR biodosimetry. Developments also are underway from other funding aimed at producing a food and drug administration approved field deployable dosimeter based on in vivo EPR measurements of incisor teeth in situ, using minimally trained, nonexpert operators to obtain immediate read-out of results.

The remainder of this discussion focuses on these minimal or noninvasive uses of EPR for biodosimetry for triage.

In great part because EPR of teeth and nails are physically based biodosimetric methods, they have a number of potential characteristics that make them especially suitable for initial triage of large-scale radiation events (Swartz et al. 2007). These include:

1. They are based on physical processes that are not confounded by most types of trauma and stress (including the injuries most likely to occur in a major radiation exposure event). Major physical changes to the teeth or nails that might impact the ability to detect dose, e.g., charring from heat, should be readily apparent.
2. The measurable effect of radiation on the teeth or nails occurs instantaneously upon exposure, is independent of the rate of exposure, and reflects the cumulative dose, albeit only at the site of the nails and teeth.
3. The measurements can be made immediately and throughout the time after the event during which initial triage and assessment for ARS would be pertinent (i.e., measurements on nails can be made up to several weeks after exposure and can be made indefinitely on teeth) (Williams et al. 2011; Black and Swarts 2010; Desrosiers and Schauer 2001; Symons et al. 1995; Trompier et al. 2009).

4. Since the in vivo measurements are nondestructive, repeated measurements can be made as needed.

5. Measurements of teeth and in vivo nails can be carried out nearby the event (i.e., the instrument if deployable), analysis at a distant laboratory is unnecessary, with immediate readout of the estimated dose after measurement (Williams et al. 2011). Measurements of ex vivo nail clippings can be adapted for detailed analysis and archival storage at distant laboratories when the logistics of the situation make such analyses feasible.

6. With the exception of the ex vivo analysis of nail samples (these require simple clippings), measurements are noninvasive.

7. Measurements using teeth and nails from multiple limbs can be used to compare estimates of the dose at multiple anatomical sites (or in combination with other biodosimetry methods); thereby providing evidence whether exposure is homogeneous or heterogeneous.

8. EPR dosimetric measurements can be made with throughput times from measurement to results of less than 6 min per subject, with devices deployed to the locale at or nearby the event and which are being developed to be operated by nonexpert personnel, after minimal training (e.g., based on a few minute video) (Williams et al. 2011).

9. Because the method is based on physical changes, patients undergoing therapeutic whole-body irradiation (or involving exposure to the teeth and/or nails) are suitable test subjects, providing a means to directly test the effectiveness of measurements made in human subjects who were irradiated in vivo. (Biologically based biodosimetric techniques, in contrast, are typically confounded by diseases and treatments, such as chemotherapy; consequently, most of their development and testing must be done in irradiated animals or with ex vivo irradiation of human samples).

The physically based biodosimetric techniques have, however, other characteristics that are likely to limit their applicability in some situations:

1. They assess dose at the specific site that is measured (i.e., in the teeth or nails) and do not reflect the individual’s specific biological reactions to the exposure. While only knowing the dose (rather than reactions to injury) is sufficient to inform initial triage decisions, it is a disadvantage for secondary stages of triage and especially in individualizing decisions about medical treatment.

2. They provide only total cumulative dose over the period when the radicals interrogated are stable. Thus, if there had been significant prior exposure to the measured sites within the sensitive time of the technique (which is indefinite for teeth and several weeks for nails), the predicted dose from the event would be overestimated.

3. While the EPR techniques have sufficient resolution for initial triage (e.g., within a half a gray of the cutoff for triage, which is usually two gray), to date, they

have not been demonstrated to have sufficient dose resolution to guide medical treatment *after* the initial triage step.

4. Some individuals may not be able to be measured. For example, vivo tooth dosimetry requires the presence of enamel on a suitable tooth (i.e., without resin or caps over the surface), while ex vivo nail clipping dosimetry requires sufficient nail length to clip.

5. Because of the paucity of hydrogen nuclei in enamel, EPR tooth dosimetry cannot directly measure dose from neutrons. However, if EPR is used in conjunction with complementary measurements that are affected by both neutrons and gamma, EPR's insensitivity to neutrons could offer an advantage by allowing differential determination of how much of the exposure was due to neutrons versus gamma radiation.

Pulling it together: the characteristics of different types of biodosimetry that best address the needs in the three scenarios involving unknown radiation exposures

Biodosimetry, i.e., providing assessment of dose at the individual level, is likely to be valuable for all three scenarios—small- and large-scale events involving potentially acute symptoms from exposures to radiation and, while not detailed here, for long-term risk assessment. The differences in needs pertain to their varying types of information that is needed, the needs for precision in the estimates, and the logistical concerns for obtaining and using the information.

Biodosimetry techniques required for small events, where the possibility of monitoring and treating all victims is feasible, need to provide information to determine whether therapeutic intervention is needed and, if so, then also to help monitor the effectiveness of the interventions. Triage per se is not needed, and it is feasible to use methods that require expertise and specialized facilities. In contrast, in large-scale events, the information needed for initial triage is to identify and severely reduce the number of people who must enter the healthcare system. However, even for people who are triaged out of health care, their results, if valid at lower levels of exposure, can be useful for long-term surveillance of health consequences.

Needs for small-scale events and secondary triage of large-scale events

Approaches well suited for small-scale events include those that are accurate to within about 0.5 Gy (the precision needed for differential clinical decision making) and along a continuum from ~1 to >10 Gy. It becomes fully feasible also to use methods based on changes in WBCs. Response for small-scale events would potentially benefit from using methods that can indicate the individual's biological response to the dose. Thus, biologically based biodosimetry would be especially useful, while physically based biodosimetry would be less applicable. Secondary (advanced) triage for large-scale events where the focus is on dose assessments shares some of the characteristics of biodosimetry for small-scale events, if the goal of the initial triage, i.e., to significantly reduce the number of people needing to

be further assessed and treated in the healthcare system, is reached such that the number is consistent with the capacity to provide effective care. In this situation, estimates of the biological implications of the dose will be especially valuable.

In addition, because many small incidents involve mishandling of radiation sources, exposures may be very asymmetric. In such cases, there is a special need for biodosimetry techniques that can determine localized doses to the affected areas. For example, EPR dosimetry of nails has been very valuable in determining doses delivered to fingers from handling sources (Trompier et al. 2011).

Needs for large-scale events

In large-scale incidents, there is a different critical need to identify people, through initial triage, who do not require immediate medical attention for radiation injury. There is also a need for secondary (advanced) stages of triage decision making to further insure that people tri-aged initially for care have in fact received a dose above the cutoff and then for a more refined estimate of dose received and determining the biological responses to injury in order to guide medical management. (It may be necessary and probably adequate for the initial stage of triage to include using dose estimates from representative samples of people who were exposed under similar conditions, measuring some and extrapolating to people who were known to be in the same location at the time of the event).

Methods for initial triage need to have the capacity to obtain the sample and then provide the results to the decision makers for triage during the window of time for initial triage, i.e., from about 1 to 7 days. Initial triage will require only modest dose resolution, since it should focus on whether the individual has received more or less than the cutoff for initial triage, usually considered to be 2 Gy, although higher values might be used. Highly desirable characteristics of methods for initial triage in large-scale events include:

- **a.** They can be applied reliably at any time after the event (i.e., it is undesirable to need to wait for a response to evolve).
- **b.** The results of the measurements are immediately available after the measurement.
- **c.** They do not require expert personnel to collect in vitro samples (or to measure if method is in vivo) or require specialized facilities and experts to analyze the samples.
- **d.** They do not require transporting samples to a distant site because of the potentially overwhelming logistical considerations such as limited transport and coordination problems, which would make it difficult to reconnect results to the individual at a time after the original sampling or measurement.

With only two possible exceptions (i.e., c-H2AX and micronuclei, (Garty et al. 2010; Turner et al. 2011)), these requirements for timing and the logistical constraints make it very challenging to use biologically based biodosimetry or WBC-based dosimetry for initial triage. On the other hand, physically based biodosimetry is likely to be especially useful for the initial triage. The radiation-induced changes detected by these techniques occur

immediately after the exposure occurs. It is feasible to make the measurements in the field, and these are not likely to be confounded by concurrent or prior pathophysiology or individual variations.

Criteria for accuracy for deciding on techniques suitable for initial triage should be weighed toward avoiding false negatives (inappropriately turning people away from further assessment or treatment). Still, of course, even for initial triage, there will be a strong advantage from combining dose estimates by one or more biodosimetric techniques with any and all other information that helps to assess whether the individual has a reasonable probability of having received a dose that can lead to significant short-term effects and can therefore could benefit from entering the healthcare system or being further evaluated.

On the other hand, false positives at initial triage (falsely identifying people to obtain secondary assessments) are more acceptable because these will have a good chance of being reversed at the secondary triage stages. In the second stage of triage, individuals who have been initially triaged into the system are further assessed for the extent of their exposure and the presence of radiation-induced injury to determine the level of care that they will need. This stage includes recognizing the possibility that some will be found to be "false positives," i.e., who do not need immediate care and therefore can be removed from the system.

The needs for dosimetry at this secondary stage of triage will be significantly different than those for initial triage (dose resolution and biological implications for the individual will be more important), and the circumstances will be more similar to small-scale events (because of the smaller number of subjects and the location in a clinical care setting). Therefore, secondary triage may be best carried out where expert personnel, and facilities are available directly or by transfer of samples or victims. Transportation of samples to distant sites will be more feasible because of the relaxation of the need to get prompt results and the feasibility of getting the results back to wherever the subject is located. Biologically based biodosimetry may be especially useful for this advanced stage of triage because multiple samples can be taken. In this stage, the potential for biologically based biodosimetry to indicate the biological implications of the dose also will be potentially very valuable. In this setting, the white cell-based techniques also will be more feasible, although for those with limited throughput, their use may still be challenged by several hundred or more subjects.

Needs for long-term risk assessment

The characteristics for biodosimetry for estimating long-term risks require biodosimetric techniques that can measure low doses and samples that remain valid for many years. Unlike the needs for dosimetry for acute injury, the techniques can involve considerable processing and specific expertise. These very special requirements and procedures have led to the use of two principal approaches for this scenario: the use of long-lasting cytogenetic changes, especially FISH, and in vitro EPR of enamel isolated from exfoliated teeth (see Kleinerman et al. 2006; Fattibene and Callas 2010). While not generally addressed in the context of focusing on acute health problems, preparations suitable to use samples later on for long-term assessments are appropriate to plan in advance so that the information is not lost.

Conclusion

The needs for the different accidental scenarios vary significantly. By considering these needs, the most appropriate biodosimetric approaches can and should be utilized when available. In all three scenarios, all available sources of information should be utilized to the extent that they are available, including clinical signs and symptoms. In particular, dose estimates at specific geographic points, based on calculations or measurements (‘‘conventional physical dosimetry’’) not specific to individuals, may be available. It also is likely that, regardless of any official guidelines to the contrary, decisions to triage individual subjects will occasionally need to be based on measurements of other individuals who were in similar exposure situations and can therefore be expected to have had the same exposure, including families that were together and people in the same room at the time of the exposure. For large-scale events, we conclude that physically based biodosimetry should be especially useful in the very early phase of a large-scale event for initial triage, while biologically based biodosimetry may be especially useful for guiding therapeutic interventions after the initial triage.

Acknowledgments

This research has been supported by a grant from NIH (U19-AI-91173). EPR tooth dosimetry was performed as part of contract HHSO100201100024C with the Biomedical Advanced Research and Development Authority (BARDA), within the Office of the Assistant Secretary for Preparedness and Response, US Department of Health and Human Services.

References

Ainsbury EA, Bakhanova E, Barquinero JF, Brai M, Chumak V, Correcher V, Darroudi F, Fattibene P, Gruel G, Guclu I, Horn S, Jaworska A, Kulka U, Lindholm C, Lloyd D, Longo A, Marrale M, Monteiro Gil O, Oestreicher U, Pajic J, Rakic B, Romm H, Trompier F, Veronese I, Voisin P, Vral A, Whitehouse CA, Wieser A, Woda C, Wojcik A, Rothkamm K. Review of retrospective dosimetry techniques for external ionising radiation exposures. Radiat Prot Dosim. 2011; 147:573–592.

Alexander GA, Swartz HM, Amundson SA, Blakely WF, Buddemeier B, Gallez B, Dainiak N, Goans RE, Hayes RB, Lowry PC. BiodosEPR-2006 meeting: acute dosimetry consensus committee recommendations on biodosimetry applications in events involving uses of radiation by terrorists and radiation accidents. Radiat Meas. 2007; 42:972–996.

Bassinet C, Trompier F, Clairand I. Radiation accident dosimetry on glass by TL and EPR spectrometry. Health Phys. 2010a; 98:400–405. [PubMed: 20065712]

Bassinet C, Trompier F, Clairand I. Radiation accident dosimetry on electronic components by OSL. Health Phys. 2010b; 98:440–445. [PubMed: 20065718]

Beinke C, Barnard S, Boulay-Greene H, De Amicis A, De Sanctis S, Herodin F, Jones A, Kulka U, Lista F, Lloyd D, Martigne P, Moquet J, Oestreicher U, Romm H, Rothkamm K, Valente M, Meineke V, Braselmann H, Abend M. Nato dosimetry study: laboratory intercomparison of the dicentric chromosome analysis assay. Radiat Res. 2013; 180:129–137. [PubMed: 23862730]

Black PJ, Swarts SG. Ex vivo analysis of irradiated fingernails: chemical yields and properties of radiation-induced and mechanically-induced radicals. Health Phys. 2010; 98:301–308. [PubMed: 20065698]

Brengues M, Paap B, Bittner M, Amundson S, Seligmann B, Korn R, Lenigk R, Zenhausern F. Biodosimetry on small blood volume using gene expression assay. Health Phys. 2010; 98:179–185. [PubMed: 20065681]

Buddemeier BR. Reducing the consequences of a nuclear detonation: recent research. Bridge. 2010; 40:28–38.

Buddemeier, BR., Dillon, MB. Key response planning factors for the aftermath of nuclear terrorism. LLNL-TR-410067. Lawrence Livermore National Laboratory (LLNL); Berkeley: 2009.

Centers for Disease Control and Prevention (CDC). Emergency preparedness and response. Specific hazards. Radiation. Acute radiation syndrome: A fact sheet for physicians. 2006. http://www.bt.cdc.gov/radiation/arsphysicianfactsheet.asp (Accessed 28 October 2013)

Coleman CN, Hrdina C, Bader JL, Norwood A, Hayhurst R, Forsha J, Yeskey K, Knebel A. Medical response to a radiologic/nuclear event: integrated plan from the office of the assistant secretary for preparedness and response, department of health and human services. Ann Emerg Med. 2009; 53:213–222. [PubMed: 18387707]

Coy SL, Cheema AK, Tyburski JB, Laiakis EC, Collins SP, Fornace A Jr. Radiation metabolomics and its potential in biodosimetry. Int J Radiat Biol. 2011; 87:802–823. [PubMed: 21692691]

Demidenko E, Williams BB, Swartz HM. Radiation dose prediction using data on time to emesis in the case of nuclear terrorism. Radiat Res. 2009; 171:310–319. [PubMed: 19267558]

Desrosiers M, Schauer DA. Electron paramagnetic resonance (EPR) biodosimetry. Nucl Instrum Methods B. 2001; 184:219–228.

DeWitt R, Klein D, Yukihara E, Simon S, McKeever S. Optically stimulated luminescence (OSL) of tooth enamel and its potential use in post-radiation exposure triage. Health Phys. 2010; 98:432–439. [PubMed: 20065717]

DiCarlo AL, Maher C, Hick JL, Hanfling D, Dainiak N, Chao N, Bader JL, Coleman CN, Weinstock DM. Radiation injury after a nuclear detonation: medical consequences and the need for scarce resources allocation. Disaster Med Public Health Prep. 2011; 5(Suppl 1):S32–S44. [PubMed: 21402810]

Flood, AB., Nicolalde, RJ., Williams, BB., Demidenko, E., Evans, J., Greene, MA., Swartz, HM. Comparative evaluation of dosimetric methods for triage in large-scale radiation events; Proceedings STO-MP-HFM-223: NATO symposium on biological effects of ionizing radiation exposure and countermeasures: current status and future perspectives; Ljubljana, Slovenia. 2012. Paper 34: MP-HFM-223-34http://www.cso.nato.int/abstracts.aspx?RestrictRDP=4 (Accessed 28 Oct 2013)

Fattibene P, Callens F. EPR dosimetry with tooth enamel: a review. Appl Radiat Isot. 2010; 68:2033–2116. [PubMed: 20599388]

Fenech M. Current status, new frontiers and challenges in radiation biodosimetry using cytogenetic, transcriptomic and proteomic technologies. Radiat Meas. 2011; 46:737–741.

Fenech M, Kirsch-Volders M, Rossnerova A, Sram R, Romm H, Bolognesi C, Ramakumar A, Soussaline F, Schunck C, Elhajouji A, Anwar W, Bonassi S. HUMN project initiative and review of validation, quality control and prospects for further development of automated micronucleus assays using image cytometry systems. Int J Hyg Environ Heal. 2013; 216:541–552.

Flood AB, Nicolalde RJ, Demidenko E, Williams BB, Shapiro A, Wiley AL Jr, Swartz HM. A framework for comparative evaluation of dosimetric methods to triage a large population following a radiological event. Radiat Meas. 2011; 46:916–922. [PubMed: 21949481]

Garty G, Chen Y, Salerno A, Turner H, Zhang J, Lyulko O, Bertucci A, Xu Y, Wang H, Simaan N. The RABIT: a rapid automated biodosimetry tool for radiological triage. Health Phys. 2010; 98:209–217. [PubMed: 20065685]

Goans, RE. Clinical care of the radiation-accident patient: Patient presentation, assessment, and initial diagnosis. In: Ricks, RC.Berger, ME., O'Hara, FM., Jr, editors. The Medical Basis for Radiation-Accident Preparedness: The Clinical Care of Victims. Parthenon; New York: 2002. p. 11-22.

Goans RE, Holloway EC, Berger ME, Ricks RC. Early dose assessment in criticality accidents. Health Phys. 2001; 81:446–449. [PubMed: 11569639]

González AJ. An international perspective on radiological threats and the need for retrospective biological dosimetry of acute radiation overexposures. Radiat Meas. 2007; 42:1053–1062.

Gougelet RM, Rea ME, Nicolalde RJ, Geiling JA, Swartz HM. The view from the trenches: Part 1-emergency medical response plans and the need for EPR screening. Health Phys. 2010; 98:118–127. [PubMed: 20065673]

Grace MB, Moyer BR, Prasher J, Cliffer KD, Ramakrishnan N, Kaminski J, Coleman CN, Manning RG, Maidment BW, Hatchett R. Rapid radiation dose assessment for radiological public health emergencies: roles of NIAID and BARDA. Health Phys. 2010; 98:172–178. [PubMed: 20065680]

He X, Swarts SG, Demidenko E, Flood AB, Grinberg O, Gui J, Mariani M, Marsh SD, Ruuge AE, Sidabras JW, Tipikin D, Wilcox DE, Swartz HM. Development and validation of an ex vivo electron paramagnetic resonance fingernail biodosimetric method. Radiat Prot Dosim. 2014 (accepted).

Horn S, Rothkamm K. Candidate protein biomarkers as rapid biomarkers of radiation exposure. Radiat Meas. 2011; 46:903–906.

Kleinerman RA, Romanyukha AA, Schauer DA, Tucker JD. Retospective assessment of radiation exposure using biological dosimetry: chromosome painting, electron paramagnetic resonance, and glycophorin-A assay. Radia Res. 2006; 166:287–302.

Lloyd DC, Edwards AA, Moquet JE, Guerrero-Carbajal YC. The role of cytogenetics in early triage of radiation casualties. Appl Radiat Isot. 2000; 52:1107–1112. [PubMed: 10836413]

Marchetti F, Coleman MA, Jones IM, Wyrobek AJ. Candidate protein biodosimeters of human exposure to ionizing radiation. Int J Radiat Biol. 2006; 82:605–639. [PubMed: 17050475]

McKeever SWS, Botter-Jensen L, Agersnap Laresen N, Duller GAT. Temperature dependence of OSL decay curves: experimental and theoretical aspects. Radiat Meas. 1997; 27:161–179.

McNamee JP, Flegal FN, Green HB, Marro L, Wilkins RC. Validation of the cytokinesis-block micronucleus (CBMN) assay for use as a triage biological dosimetry tool. Radiat Prot Dosim. 2009; 135:232–242.

Muznyk NA, Wilkins RC, Carr Z, Lloyd DC. The capacity, capabilities and needs of the WHO biodosenet member laboratories. Radiat Prot Dosim. 2012; 151:611–620.

Nicolalde, RJ., Flood, AB., Watts, BV., Swartz, HM., Ma, LE., Toler, AJ., Gougelet, RM. A decision support tool for evaluating the effectiveness and logistic consideration of biodosimetry methods; Proceedings STO-MP-HFM-223: NATO symposium on biological effects of ionizing radiation exposure and countermeasures: current status and future perspectives; Ljubljana, Slovenia. 2012. Paper 34: MP-HFM-223-35http://www.cso.nato.int/abstracts.aspx?RestrictRDP=4. (Accessed 28 Oct 2013)

Ossetrova NI, Sandgren DJ, Gallego S, Blakely WF. Combined approach of hematological biomarkers and plasma protein saa for improvement of radiation dose assessment triage in biodosimetry applications. Health Phys. 2010; 98:204–208. [PubMed: 20065684]

Parker DD, Parker JC. Estimating radiation dose from time to emesis and lymphocyte depletion. Health Phys. 2007; 93:701–704. [PubMed: 17993851]

Paul S, Amundson SA. Development of gene expression signatures for practical radiation biodosimetry. Int J Radiat Oncol Biol Phys. 2008; 71:1236–1244. [PubMed: 18572087]

Phillips M, Byrnes R, Cataneo RN, Chaturvedi A, Kaplan PD, Libardoni M, Mehta V, Mayur M, Patel U, Ramakrishna N, Schiff PB, Zhang X. Detection of volatile biomarkers of therapeutic radiation in breath. J Breath Res. 2013; 7:036002. (8 pp). doi: 10.1088/1752-7155/7/3/036002 [PubMed: 23793046]

Pinto MM, Santos NF, Amaral A. Current status of biodosimetry based on standard cytogenetic methods. Radiat Environ Bioph. 2010; 49:567–581.

Rana S, Kumar R, Sultana S, Sharma RK. Radiation-induced biomarkers for the detection and assessment of absorbed radiation doses. J Pharm Bioallied Sci. 2010; 2:189–196. [PubMed: 21829314]

Rea ME, Gougelet RM, Nicolalde RJ, Geiling JA, Swartz HM. Proposed triage categories for large-scale radiation incidents using high-accuracy biodosimetry methods. Health Phys. 2010; 98:136–144. [PubMed: 20065675]

Romm H, Wilkins RC, Coleman CN, Lillis-Hearne PK, Pellmar TC, Livingston GK, Awa AA, Jenkins MS, Yoshida MA, Oestreicher U, Prasanna PG. Biological dosimetry by the triage dicentric chromosome assay: potential implications for treatment of acute radiation syndrome in radiological mass casualties. Radiat Res. 2011; 175:397–404. [PubMed: 21388284]

Romm H, Barnard S, Boulay-Greene H, De Amicis A, De Sanctis S, Franco M, Herodin F, Jones A, Kulka U, Lista F, Martigne P, Moquet J, Oestreicher U, Rothkamm K, Thierens H, Valente M,

Vandersickel V, Vral A, Braselmann H, Meineke V, Abend M, Beinke C. Nato biodosimetry study: laboratory intercomparison of the cytokinesis-block micronucleus assay. Radiat Res. 2013; 180:120–128. [PubMed: 23862731]

Rothkamm K, Beinke C, Romm H, Badie C, Balagurunathan Y, Barnard S, Bernard N, Boulay-Greene H, Brengues M, De Amicis A, De Sanctis S, Greither R, Herodin F, Jones A, Kabacik S, Knie T, Kulka U, Lista F, Martigne P, Missel A, Moquet J, Oestreicher U, Peinnequin A, Poyot T, Roessler U, Scherthan H, Terbrueggen B, Thierens H, Valente M, Vral A, Zenhausern F, Meineke V, Braselmann H, Abend M. Comparison of established and emerging biodosimetry assays. Radiat Res. 2013; 180:111–119. [PubMed: 23862692]

Sholom S, Chumak V. EPR emergency dosimetry with plastic components of personal goods. Health Phys. 2010; 98:395–399. [PubMed: 20065711]

Sholom S, DeWitt R, Simon S, Bouville A, McKeever S. Emergency optically stimulated luminescence dosimetry using different materials. Radiat Meas. 2011; 46:1866–1869. [PubMed: 22125409]

Swartz HM, Burke G, Coey M, Demidenko E, Dong R, Grinberg O, Hilton J, Iwasaki A, Lesniewski P, Kmiec M, Lo K, Nicolalde RJ, Ruuge A, Sakata Y, Sucheta A, Walczak T, Williams BB, Mitchell CA, Romanyukha A, Schauer DA. In vivo EPR for dosimetry. Radiat Meas. 2007; 42:1075–1084. [PubMed: 18591988]

Swartz HM, Flood AB, Gougelet RM, Rea ME, Nicolalde RJ, Williams BB. A critical assessment of biodosimetry methods for large-scale incidents. Health Phys. 2010; 98:95–108. [PubMed: 20065671]

Swartz HM, Williams BB, Nicolalde RJ, Demidenko E, Flood AB. Overview of biodosimetry for management of unplanned exposures to ionizing radiation. Radiat Meas. 2011; 46:742–748.

Symons MC, Chandra H, Wyatt JL. Electron paramagnetic resonance spectra of irradiated finger-nails: a possible measure of accidental exposure. Radiat Prot Dosim. 1995; 58:11–15.

Trompier F, Romanyukha A, Kornak L, Calas C, LeBlanc B, Mitchell C, Swartz H, Clairand I. Electron paramagnetic resonance radiation dosimetry in fingernails. Radiat Meas. 2009; 44:6–10.

Trompier F, Bassinet C, Clairand I. Radiation accident dosimetry on plastics by EPR spectrometry. Health Phys. 2010; 98:388–394. [PubMed: 20065710]

Trompier F, Bassinet C, Della Monaca S, Romanyukha A, Reyes R, Clairand I. Overview of physical and biophysical techniques for accident dosimetry. Radiat Prot Dosim. 2011; 144:571–574.

Trompier, F., Fattibene, P., Woda, C., Bassinet, C., Bortolin, E., De Angelis, C., Della Monaca, S., Viscomi, D., Wieser, A. Retrospective dose assessment in a radiation mass casualty by EPR and OSL in mobile phones. 2013. IRPA13 2358609http://www.irsn.fr/EN/Research/publications-documentation/Publications/DRPH/Documents/2358609%20TROMPIER%20papier.pdf. (Accessed 28 Oct 2013)

Turner HC, Brenner DJ, Chen Y, Bertucci A, Zhang J, Wang H, Lyulko OV, Xu Y, Shuryak I, Schaefer J, Simaan N, Randers-Pehrson G, Yao YL, Amundson SA, Garty G. Adapting the c-H2AX assay for automated processing in human lymphocytes. 1 technological aspects. Radiat Res. 2011; 175:282–290. [PubMed: 21388271]

US Department of Health & Human Services. Radiation emergency medical management (REMM). Dose estimator for exposure: 3 biodosimetry Tools. 2013. http://www.remm.nlm.gov/ars_wbd.htm. (Accessed 28 Oct 2013)

Vaurijoux A, Gruel G, Pouzoulet F, Gregoire E, Martin C, Roch-Lefevre S, Voisin P, Voisin P, Roy L. Strategy for population triage based on dicentric analysis. Radiat Res. 2009; 171:541–548. [PubMed: 19580489]

Waselenko JK, MacVittie TJ, Blakely WF, Pesik N, Wiley AL, Dickerson WE, Tsu H, Confer DL, Coleman CN, Seed T, Lowry P, Armitage JO, Dainiak N, Strategic National Stockpile Radiation. Working group medical management of the acute radiation syndrome: recommendations of the strategic national stockpile radiation working group. Ann Intern Med. 2004; 140:1037–1051. [PubMed: 15197022]

Williams BB, Dong R, Flood AB, Grinberg O, Kmiec M, Lesniewski PN, Matthews TP, Nicolalde RJ, Raynolds T, Salikhov I, Swartz HM. A deployable in vivo EPR tooth dosimeter for triage after a radiation event involving large populations. Radiat Meas. 2011; 46:772–777. [PubMed: 21966241]

Wojcik A, Lloyd D, Romm H, Roy L. Biological dosimetry for triage of casualties in a large-scale radiological emergency: capacity of the EU member states. Radiat Prot Dosim. 2010; 138:397–401.

Yordanov ND, Gancheva V, Georgieva E. EPR and UV spectroscopic study of table sugar as a high-dose dosimeter. Radiat Phys Chem. 2002; 65:269–276.

Yukihara EG, Mittani J, McKeever SWS, Simon SL. Optically stimulated luminescence (OSL) of dental enamel for retrospective assessment of radiation exposure. Radiat Meas. 2007; 42:1256–1260. [PubMed: 19623269]