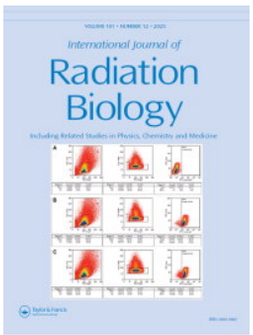

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REVIEW

Perspectives of IABERD on biodosimetry strategies for a large-scale nuclear event

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ABSTRACT

Purpose: Performing biodosimetry assessment for several hundreds of thousands of individuals in the aftermath of large scale radiological/nuclear incidents will be technically challenging. The purpose of this review is to provide logistical planning to determine when, how and which biodosimetry tools can be used for providing useful information to mediate an effective triage and for guiding the medical management of exposed victims of such an event. **Conclusions:** This review highlighted the potential capabilities of various types of biodosimetry tools in advanced development to handle the needs of different triage stages for a large-scale nuclear detonation event. While each was reviewed independently, the consensus was that complex exposure scenarios require a multiparametric approach where biomarkers/biodosimeters can be used alternatively or targeted for subgroups, e.g. with combined injury or by type of radiation, for rapid assessment and confirmation of exposure dose for exposed individuals. Further studies and exercises are required to validate the capability of using the biodosimetry tools, both individually and in combination, under the likely logistical constraints of a nuclear detonation, both to guide development of processes such as high-throughput platforms and field-deployable mechanisms that can best address the volume and needs of the affected population.

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Large scale nuclear/radiological incidents; triage; radiation biodosimetry; electron paramagnetic resonance; gene expression; metabolomics

Introduction

This manuscript marks the beginning of a series of manuscripts to be developed by the member experts of the International Association for Biological and EPR Radiation Dosimetry (IABERD) to describe the optimal use of biodosimetry tools for various scenarios involving accidental or intentional exposure to ionizing radiation with the intent to harm or terrorize the impacted population. IABERD is a nonprofit scientific organization officially established in 2011 to promote collaborative research, development, and education in biological dosimetry and electron paramagnetic resonance (EPR) spectroscopy applied to ionizing radiation. Its primary mission is to coordinate and promote activities in these fields at an international level (https://iaberd.org/index.php/iaberd-association/).

The series is intended to provide guidance for using biodosimetry tools for different exposure scenarios as defined by the number of individuals involved and the associated logistics for triaging them to receive immediate medical attention. The series is expected to cover a broad definition of biodosimetry techniques, including those currently in advanced developmental stages. The intent is to discuss their strengths and challenges in the context of each exposure scenario and to summarize recent developments in the biodosimetry field.

This manuscript, the first of the series, focusses on the readiness of biodosimetry for large nuclear events that will potentially expose several thousands to millions of people to combined external exposures of gamma rays from the direct blast/fallout and neutrons from the direct blast. Biodosimetry

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usage for other types of ionizing radiation exposures (e.g. radiation accidents involving single or mixed beams, chronic exposures, or internal exposures) and radiation qualities (e.g. alpha and beta) will be addressed in future manuscripts.

Basic types of radiation biodosimetry for large-scale events

The term 'biodosimetry' used in this manuscript is inclusive of clinical signs/symptoms, measurement of changes in macromolecules/biological processes in cells/tissues as well as detection of stable free radicals in the materials of biological origin such as nails and teeth for estimating the absorbed dose in radiation exposed individuals. Radiation biodosimetry is an actively growing field and research over the last several decades has yielded a battery of biodosimetry tools with varying levels of sensitivity and specificity for absorbed dose estimation. Although several biodosimetry tools are currently available for some uses or are in advanced development and evaluation stages, none has been approved by regulatory authorities for use in large-scale incidents nor tested in very large-scale exercises.

In the case of large-scale radiological/nuclear incidents, several thousands of individuals are likely to receive considerable doses of radiation. Biodosimetry can help in triaging victims based on exposure levels, thereby guiding appropriate medical treatment for those who are at an increased risk for developing acute radiation syndrome (ARS). More specifically, biodosimetry can be used to categorize victims based on their likelihood of benefitting from ARS-related care (i.e. including both mitigators and treatments): (I) no or only palliative care is appropriate for victims of high dose exposures who are unlikely to survive (> 6 Gy), (II) mitigators and/or active treatment are needed for individuals with exposures exceeding 2 Gy, and (III) no medical treatment for low or no exposure (< 2 Gy) where victims have high survivability without care. Besides exposure dose categorization, biodosimetry can also provide useful information about uniform or non-uniform exposure in the affected individuals. Biodosimetry can also support evaluation of long-term health risks for delayed effects of radiation such as cancer and genetic alterations, but this aspect will not be further elaborated here.

Special considerations for large-scale events

In addition to meeting the criteria for sensitivity, specificity and reliability, biodosimetry assays/techniques need to be vigorously tested for their capacity to address various confounding factors such as age and gender, including logistical needs based on each exposure scenario. Logical considerations for biodosimetry to be used in large scale events include its capacity for scalability to meet the high-volume demands, the reproducibility of results across different laboratories or devices, and the adequacy of the laboratory infrastructure in terms of trained personnel, materials and reagents to perform the volume within a reasonable timeframe (days to weeks). For large nuclear events, the general infrastructure is likely to be seriously compromised by disruption of transportation into and out of the incident area, communication interruptions, limited food supplies, power outage and limited sheltering facilities for holding victims while awaiting triage decisions. The nature of a large nuclear explosion implies that radiation exposure levels leading to ARS will most likely involve external gamma ray exposure but will also involve neutrons if victims are in the direct blast zone. Some victims may have partial body exposure due to their position at the time of exposure, and many may have combined injury (radiation plus concurrent thermal burns or injury) if located in the direct blast zones.

The exposure scenario

A large-scale nuclear event can occur by either an improvised nuclear device (IND) in an urban setting or armed conflict involving the utilization of a nuclear weapon. The potential for these events has been increased by the emergence of geopolitical instability and nuclear threats all around the globe. To estimate the volume of casualties that could occur in a nuclear event, researchers have simulated a likely scenario if a 1 kT or 10 kT nuclear bomb were detonated over a large metropolitan city with a population of 2 million (Waselenko et al. 2004). Simulations include characteristics of a nuclear explosion as well as the structures in which people are located and weather patterns that would likely impact the dose and injuries received by the population located in the direct blast zones and/or in dangerous fallout zones. In general, people in the areas directly in the region of the blast will have higher rates of physical injuries and burns and/or radiation from neutrons and gamma rays, in comparison to people located in areas with dangerous fallout who may only be exposed to gamma rays. Sheltering, particularly in areas where structures did not receive damage from the blast, and partial shielding within structures, even in the blast area, could lead to variation in the dose received resulting in partial-body exposure rather than full-body exposure. Internal radiation exposure, while possible, is not likely to be a major factor in this scenario. A few past reviews discussed the logistical steps for the allocation of scarce resources, medical planning/response and emergency response guidance for the first 48 hrs after nuclear detonation (Knebel et al. 2011; Coleman et al. 2012; Musolino et al. 2013; Buddemeier et al. 2018).

Using casualty numbers from the simulations of a 10 kT detonation in New York City (NYC) and restricting the population to people located in the blast and dangerous fallout zones, the number of survivors eligible for triage decision-making (i.e. not already dead or 'expectant') would be more than 1.5 million people in the direct blast zones and 1.4 million more in dangerous fallout zones (Waselenko et al. 2004). If people in the immediate NYC area outside of these zones were also considered for dosimetry assisted triage, an additional several million people would be included. In addition to the burden of dealing with such an overwhelming number of cases, the basic infrastructure, including any healthcare or laboratory facilities will be severely damaged or hampered in the incident site/region. Clearly, these numbers are overwhelming and emergency planning for triage

needs to be prepared to severely reduce the targeted population for triage by dosimetry and subsequent ARS care. Lessons from the 911 terrorist attack in NYC in 2001 and the earthquake/tsunami/nuclear power plant meltdown in Japan in 2011 have taught us that chaos, exacerbated by fear and confusion, will greatly hamper emergency response processes. This will especially occur in a nuclear detonation when a military response and additional hostilities are imminently likely. We briefly review how these factors will impact choices for using biodosimetry for triage in this scenario.

To evaluate what potential roles biodosimetry can play in triage, we should consider how the medical response system will be organized. In terms of radiation risk, it is essential to first identify who may or may not have had an exposure without any risk for ARS. 'Significant risk' of ARS is usually defined as having an absorbed dose of 2 Gy or higher [assuming an acute exposure, uniformly distributed over the whole body (Grace et al. 2010; IAEA, 2015; Jaworska et al. 2015)]. The task of triaging people for radiation risk in any moderate to large event is generally expected to occur in three stages as described below:

Biodosimetry for the first stage of triage

While much of the early work in the biodosimetry field focused on developing tools for the initial stage of triage, it is timely to reassess this emphasis for large-scale nuclear events from a realistic point of view. Experience gained from conducting exercises using moderate-sized populations/samples has taught us that there are many challenges for carrying out biodosimetry in the field for a very large population, especially in view of the chaotic conditions and the limited number of previously trained responders who could assist. There also would be considerable challenges in transporting sample gathering materials and analytical devices into the areas where initial triage would occur. In view of these challenges, it would be very difficult to have any response in the first stage of triage that requires contact with each person, even after assuming that dangerous radiation zones are designated rapidly and biodosimetry is restricted to those zones.

Biological sampling (even if the sample is left in situ during *vivo* measurements) is a prerequisite for all types of biodosimetry assays. If analysis is performed in vivo, the measuring equipment needs to be moved to where the victims gather. If analysis requires in vitro samples, sample collection materials need to be provided even if the individual can collect his/her own sample by skin penetrating devices such as needles or swabs; sample collection tubes will then need to be delivered to the facility safely, with enough time for analysis so that the results can be communicated reliably back to implement timely triage or treatment decisions for the target individual. Distribution of sample collection kits to an entirely affected population and returning them for analysis, with results available for triage or treatment decisions and the entire process having been completed in a timely manner under chaotic conditions, is equally challenging. Carrying out these steps for millions of victims under compromised infrastructure and potential mass migration of people is indeed daunting.

In view of the challenges in sample collection and analysis in the field as mentioned above, exacerbated by the huge volumes anticipated in a large-scale nuclear event, many experts (Hick et al. 2018; Satyamitra et al. 2022; Swartz and Flood 2023) have concluded that biodosimetry, in the aftermath of a large-scale nuclear incident, is unlikely to provide the principal means to carry out initial triage. In the absence of biodosimetry, onset and severity of some of the clinical signs/symptoms may be useful for segregating individuals with an enhanced risk for developing ARS. While any self-reporting of the prodromal symptoms (time to emesis, diarrhea etc.) by the victims may be highly subjective, clinical evaluation for numerous people would be equally challenging. Therefore, it is highly likely that the initial triage will be based on using methods to identify geographic sites or locations where radiation doses are likely to have been of sufficient magnitude to lead to ARS; the population so identified would then constitute the group who would be evaluated at a site for secondary triage.

Biodosimetry for the second stage of triage

While some reduction can be achieved by the first stage of triage (i.e. determining who was in areas with significant risk of high doses of radiation), the number of subjects to be evaluated in the 2nd stage of triage is still very daunting but it will be relatively feasible to carry out effective biodosimetry. The role of biodosimetry in the second stage of triage is to categorize subjects into three categories: (I) palliative care only for expectants (II) receive active ARS care for moderate exposures exceeding 2 Gy, and (III) defer treatment or place them under compassionate care for low dose exposures. Early medical decisions can be made by establishing the physical dose and exposure homogeneity. Identification of individuals with partial body exposures will be important because the spared bone marrow will help victim's blood cells to recover without a bone marrow transplant thereby enabling the effective utilization of medical countermeasures on people needing urgent care. Besides determining the absorbed dose, several biodosimetry tools have the capability of distinguishing uniform exposures from partial body exposures. The logistical challenges for biodosimetry would be greatly reduced with the capabilities available at the second stage of triage. Transporting certain types of samples is likely to be less complicated since deployable analytical tools and devices may be available at these sites. However, biodosimetry needing off-site analysis would still be difficult.

This stage presumably would take place at ad hoc medical decision-making sites where some expertise and equipment could be available. It could also occur in existing medical facilities or in rapidly developed sites resembling those of first stage military medical facilities. However, sites where biodosimetry could perform these roles should minimally include a functioning infrastructure with water, power, electronic communications and other utilities; availability of significant medical and technical expertise; the ability to accommodate and utilize prepositioned materials for physical injury and/or radiation injury; and the ability to provide minimal patient care and allow temporary patient accommodation.

Biodosimetry for the third stage of triage

The third stage of triage would be aimed at refining the definitive 'biological dose' (i.e. the biological risk, including consideration of the characteristics of the individual) and starting more definitive medical steps. This stage presumably would be at a medical facility (including sites developed in response to the event) where at least the initial treatments would be carried out. The individuals entering the third stage might have had a determination that the dose is > 2 Gy and > 6 Gy. While most decisions on the types of treatment will be made by clinical evaluation of the individual, aided by clinically based systems developed to accomplish this (e.g. EAST- The Exposure and Symptom Triage and METREPOL-MEdical TREatment ProtocOLs), there may be a role for some biodosimetric techniques. These would be those that determine the biological impact of the measured dose, or whether the exposure was homogeneous, or those that provide insights into organ specific damage. Also, if subjects with physical injuries which have been stabilized and the subject then brought directly to the triage stage 3 facility, biodosimetric techniques that can measure doses as low as 0.5 Gy in physically compromised individuals could be very useful for evaluating the risk from combined injury.

It is clear from the foregoing account that an operational infrastructure involving the coordinated networks of emergency response, biodosimetry and medical management may be required for responding to a large nuclear detonation event. A schematic diagram for the coordinated activities of all the three integrated networks for different triage stages is shown in Figure 1.

Advantages and challenges of current biodosimetry tools

The advantages and challenges for each of the currently used biodosimetry tools in meeting the capabilities for the second and third stages of triage for large nuclear events are described below. Of note, some tools, while useful in other scenarios, may not be well suited for the scenario being considered here. Some of the characteristic features (longevity of signal, dose detection range, assay time for dose estimation, field deployment capability, status of clinical validation and potential limitations) of existing biodosimetry tools and those that are currently under advanced stages of development are summarized in Table 1.

Clinical biodosimetry

Clinical biodosimetry makes use of clinical signs (e.g. changes in differential [complete] blood counts [CBCs] or lymphocytes) and observed symptoms (e.g. dizziness, temperature rise, diarrhea, skin changes, and perhaps time to emesis after the event) occurring minutes to days after acute radiation exposure.

For triage following a large-scale nuclear event, clinical symptoms have the advantage that they can be readily observed or obtained by personal communication. Some symptoms, if severe, can indicate that the victims are unlikely to survive, while moderate symptoms may support triaging to receive ARS care, and their absence may indicate that the victims should be categorized under no ARS care. However, these symptoms are not necessarily specific to radiation. For example, stress or physical injuries or burns can also induce vomiting; vomiting can occur from contagion, i.e. from seeing others vomit; and the evidence for its association with linearity of dose has been questioned (Demidenko et al. 2009). This illustrates why evaluating more than one symptom is necessary to inform a triage decision with confidence.

On the other hand, clinical signs can be monitored soon after relevant radiation exposures using laboratory tests that are, in a clinical setting, ubiquitously available and 'simple' to perform, e.g. CBCs or lymphocyte depletion (Goans et al. 1997)

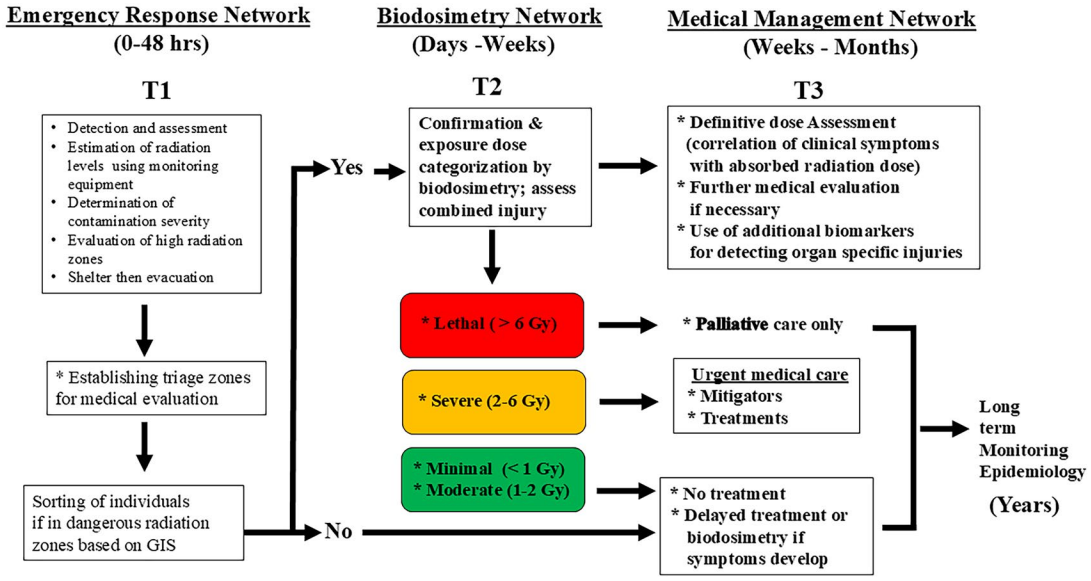

Figure 1. A schematic diagram showing the coordinated activities of the three networks (emergency response, biodosimetry and medical management) for mediating an effective triage in response to a large nuclear detonation event. The approximate timelines for each of the three triage stages (T1, T2 and T3) are given.

Table 1. Current characteristics of biodosimetry tools for potential use in large nuclear events.

Tools	Signal longevity[a]	Detection sensitivity[b]	Assay time per sample[c]	Clinical validation[d]	Field deployable[e]	Current limitations for use in very large events
Clinical biodosimeters						
Time to emesis	Min-days	1–10 Gy	Self-report/Survey 5 min	yes	yes	Some individuals may be asymptomatic despite dose (false negatives) Some individuals may have anxiety-induced vomiting (false positives) Positive correlation only with doses higher than 3 Gy
LDK	Days-weeks	0.5–10 Gy	5-10 min	yes	yes	Requires frequent blood sampling every 12 hr for up to 48 hr
NLR	Days-weeks	0.5–10 Gy	5–10 min	yes	yes	Requires frequent blood sampling every 12 hr for up to 48 hr
CBC with differential	Days-weeks	0.5–10 Gy	5–10 min	yes	yes	Requires frequent blood sampling every 12 hr for up to 48 hr
Biologically based biodosimeters						
DCA	Days-months	0.1 – 5Gy	72–96 hr	yes	no	Laborious and time-consuming; may be impractical for very large events
G0-PCC	Days-months	>20 Gy	8–12 hr	no	no	Requires expertise; only in few select laboratories; cell fusion efficiency is variable; unsuitable for mass casualties
G2-PCC	Days-months	>20 Gy	72–96 hr	no	no	Laborious and time-consuming; may be impractical for very large events
CBMN	Months-yrs	0.3–5 Gy	96 hr	yes	no	Laborious and time-consuming; may be impractical for very large events
Gene expression	1–7 days	0.1–5 Gy	3–36 hr	no	yes	Inter-individual variation due to co-morbid factors.
Micro RNA	1–7 days	0.5–5 Gy	9–18 hr	no	yes	Inter-individual variation due to co-morbid factors.
Proteomics	1–7 days	0.1–5 Gy	9–12 hr	no	no	Inter-individual variation due to co-morbid factors.
γ-H2AX	1–2 days	0.5–5 Gy	4–6 hr	no	no	Signal lost within a few hrs after external doses < 2 Gy.
Metabolomics	1–7 days	1–10 Gy	9–12 hr	no	no	Inter-individual variation due to co-morbid factors.
Na-activation in blood	1–3 days	1mGy->30 Gy	5–60 min	yes	yes	Conversion coefficients dependent on neutron spectra
P- activation in air	Wks-Mos	0.5 Gy->30 Gy	10–60 min	no	yes	Not directly field deployable
Physically based biodosimeters						
In vitro teeth EPR	0 days-lifetime	1- >30 Gy	1 hr	yes	no	Requires shed teeth or biopsy of tooth, individual variation due to UV exposure or medical exposure to radiation involving teeth. Use of tooth biopsy requires Q-band EPR equipment
In vivo teeth EPR	0 days-lifetime	1- >30 Gy	10 min	yes	yes	Requires special-use L-band EPR equipment, individual variation due to UV exposure or medical exposure to radiation involving teeth
In vitro nails EPR	0 days-weeks	1–30 Gy	10 min	yes	no	Artifacts from clipping process and from storage after clipping make it unsuitable for any stage of triage ; may be useful for monitoring of worried well using off-site analysis
In vivo nails EPR	0 days-weeks	1–30 Gy	5 min	no	yes	Requires X-Band magnet with gap of at least 2″.

Legend: LDK-lymphocyte depletion kinetics, NLR-neutrophil to lymphocyte ratio, CBC-complete blood cell counts, DCA-dicentric chromosome assay, G0-PCC- prematurely condensed chromosomes of G0 phase, G2-PCC- prematurely condensed chromosomes of G2 phase, CBMN- cytokinesis block micronucleus assay, and EPR-electron paramagnetic resonance. Na-Sodium, P-Phosphorus, Wks-Weeks, Mos-Months.

[a]Lower range is when sample is valid for collection; upper range is how long sample is valid for collection.

[b]This column reports Gy in photon equivalent exposures to account for the biological effects of neutrons, i.e. Gy is expressed as the lower and upper equivalent dose from photons (X-rays or gamma rays) that would cause the same extent of biological effect. Note: doses are assumed to be external only.

[c]Batch or simultaneous processing, including high throughput devices or AI or multiple small devices, is being developed to increase the number of samples analyzed within a short timeframe after the event. Other logistical considerations such as time to transport samples, if needed, and the availability of sufficient trained personnel and facilities to deal the biodosimetry needs are not noted here.

[d]Clinical validation refers to use in vivo in human studies.

[e]Field deployable refers to capacity to perform analyses outside of designated labs or hospitals.

or other clinical chemistry tests, e.g. C-reactive protein (CRP; Ossetrova et al. 2014). Unlike symptoms, some clinical signs such as changes in CBCs (assessed either via lymphocyte depletion test, lymphocyte to granulocyte ratio or integrated triage tools like the H-module (Port and Abend 2018), are independent of any psychological impact on the patient. Newer scientific tools like H-module are based on scientific evaluation of scarce but real data from radiation accident events and subsequently tested in alternative populations, e.g. patients with infections (Port and Abend 2018). However, they may be affected by the presence of physical injuries and burns. Moreover, resources to carry out these tests may not be always available, especially for triage decisions being made soon after the event. Evaluation of signs and symptoms for early triage are described in documents like EAST and METREPOL (Fliedner et al. 2001; Hick et al. 2018). EAST also describes using interview questions, including the location of people at the time of the event. Although a single sign or symptom or a single laboratory test may be ambiguous, a combination of different clinical findings and laboratory findings will likely increase the specificity of the assessment. Depending on the findings of an individual test, a specificity > 90% can be easily achieved even within the first 1–3 days after radiation exposure. For example, after receiving appropriate training on differential blood tests, students and postgraduates of a specialist NATO training course demonstrated they could achieve a reproducible level of sensitivity and specificity (> 90%) using a test set of patient data from real accidents (Port et al. 2021a).

In summary, the main advantage of using signs and symptoms for biodosimetry in large-scale nuclear events is their widespread availability for tests, accessibility for observation, and capability of being applied in a timely way for decision making, even without the need for any advanced

expertise or technical support. Adequate, albeit even limited, training is mandatory but easy to achieve with clinically experienced physicians. The additional and recommended use of simple laboratory tests like CBC increases the specificity and is therefore desirable to make it available for every patient in secondary or tertiary triage situations.

To effectively use clinical biodosimetry for a large-scale triage, a nationwide medical management network for radiological/nuclear emergencies needs to be established, e.g. by giving basic training about radiological effects and their management in a large-scale accident to medical students and residents. After establishing the medical management network, refresher courses can be given to maintain/sustain the skill set of the medical management workforce. Triage stage 2 is the most likely the place where the clinical signs and symptoms can be effectively employed.

Cytogenetic biodosimetry

Dicentric chromosome assay (DCA)

Dicentric chromosomes, which are induced by ionizing radiation, were first utilized by Bender and Gooch in 1962 (Bender and Gooch 1962a, 1962b) for estimating the absorbed radiation dose in individuals exposed during the Recuplex criticality accident in Hanford, WA, USA. Results of this seminal study laid the foundation for cytogenetics-based radiation biodosimetry, and subsequent studies performed since 1962 have unequivocally established the Dicentric Chromosome Assay (DCA) as the gold standard for estimating the absorbed radiation dose in scenarios involving a few cases. It is now routinely carried out in most cytogenetic biodosimetry laboratories worldwide.

DCA was used in the aftermath of some of the well-known large-scale accidents such as Chernobyl (Sevan'kaev et al. 2005), Goiania (Ramalho et al. 1995; 1998) and Fukushima-Daiichi (Suto et al. 2013; Suto 2016) for dose estimation in exposed individuals. However, when the logistic and practical considerations of handling millions of samples are considered, DCA becomes problematic. One main issue with DCA is the turnaround time of 3–4 days for dose estimation after the receipt of the blood samples in the laboratories. To expedite this process, several technological developments/improvements have been made over the last several years. Development of automated equipment for performing all the liquid handling steps involved in lymphocyte culture and chromosome preparation has certainly enabled high throughput sample processing. To address the bottleneck of dicentric chromosome scoring, several strategies have been considered. Firstly, scoring only 50 metaphase cells for dose estimation has reduced the time required for scoring (Lloyd et al. 2000; Romm et al. 2011; Wilkins et al. 2011), however, even with this triage mode of scoring (50 cells or 30 dicentrics) it would still take a considerable amount of time for the analysis of thousands of samples. Secondly, the introduction of automated metaphase image acquisition and analysis has been shown to reduce the scoring time for 150 metaphase images from 30 minutes for manual scoring down to 2 minutes demonstrating its potential as a triage tool for mass casualty incidents (Romm et al. 2013; Ryan et al. 2019). Another recent development to promote high throughput sample processing and scoring is a miniaturized version of DCA that utilizes a multi-tube matrix of 96 bar-coded 1.4 ml tubes to process 96 samples simultaneously (Balajee et al. 2018). These types of technical advances will continue to improve the feasibility of the DCA for mass casualty scenarios.

It is realized that a single cytogenetic biodosimetry laboratory, even with sufficient automation capacity, will not be able to provide dose estimates for many individuals in a timely manner. To address this issue, national and international networks of cytogenetic biodosimetry laboratories as well as technical advancements are being established (Schunck et al. 2004; Martin et al. 2007; Blakely et al. 2009; Wilkins et al. 2011; Kulka et al. 2012; García et al. 2013; Gruel et al. 2013; Romm et al. 2013; De Amicis et al. 2014; Rogan et al. 2016; Liu et al. 2017; Oestreicher et al. 2017; Romm et al. 2017; Shirley et al. 2017; Balajee et al. 2018, 2019). These networks participate in regular inter-laboratory comparison exercises to validate harmonization efforts of biodosimetry assays and to leverage the available resources for adequately responding to large-scale radiological/nuclear incidents. A survey on the international capacity for biodosimetry, conducted by the WHO in 2020, estimated the total global capacity to accept and process simultaneous samples for DCA analysis during a mass casualty event, considering available resources but not accounting for scoring time, was almost 11000/month (Wilkins et al. 2022). Furthermore, the average number of samples per laboratory that could be scored using the DCA was determined to be 188 samples per month in triage mode (Wilkins et al. 2022). Even with the addition of automated sample processing and scoring, dose estimates for the first batch of 1000 individuals/equipment will take about two weeks. Based on this approximate estimation, biodosimetry for several thousands of individuals will likely take several months, thereby obviating its usefulness for initial triage or medical management of exposed victims.

There are also some practical limits that may impact the suitability of the DCA for different stages of triage, particularly for large scale nuclear events. DCA has a dose detection range of 0.1 - 5 Gy, but the dose effect relationship is unreliable beyond 5 Gy of photons due to either increased cell death or increased growth arrest of lymphocytes at the G2/M phase of the cell cycle. The detection threshold of DCA of 0.1 Gy does not pose any major constraints since the cutoff dose for triage is 2 Gy, however, the upper limit is more of a concern.

To overcome this limitation, efforts have been made to induce prematurely condensed chromosomes from the interphase cells of either in G0 phase by cell fusion technique [inactivated Sendai virus or polyethylene Glycol (PEG)] or G2 phase by protein phosphatase inhibitors [calyculin A and okadaic acid]. Recent studies have demonstrated that calyculin A induced G2-PCCs can be used for estimating the absorbed dose at high radiation dose exposures in vitro (Wang et al. 2007; 2009; Puig et al. 2013; Sun et al. 2020b; Gotoh 2023; Sun et al. 2023). Although G2-PCCs enable dose estimation for exposures higher than 20 Gy, the turnaround time for dose

estimation using G2-PCCs is still 3–4 days (i.e. like conventional DCA). A considerably shortened version of calyculin A induced G2-PCC assay was recently demonstrated for triage by reducing the culture time of lymphocytes to 36 hrs instead of 48 hrs (Smith et al. 2024).

Research is under development to increase the throughput of PCC, either by reducing the overall processing time or increasing the number of samples that can be processed simultaneously. Using G0-PCCs, absorbed doses can be estimated within 6–8 hrs after the receipt of the blood samples excluding the time required for thawing of frozen mitotic CHO cells prior to fusion with human lymphocytes. A high throughput automatable approach for G0 PCC has been recently demonstrated (Pantelias and Terzoudi 2018) that is distinctly advantageous for large-scale incidents. This approach involves the addition of centromeric and telomeric probes by Fluorescence in situ Hybridization (FISH) to enable the detection of the centromeric regions, and since dicentrics are not easily detectable either in G0-PCCs or G2-PCCs by Giemsa staining alone (Ryan et al. 2019).

Performance of G0-PCC using the cell fusion technique has some limitations as it requires a considerable level of expertise and performing laboratories are required to maintain a stockpile of frozen high quality mitotic CHO cells for fusion. PCC is currently performed only in a few select laboratories globally. Additionally, cell fusion technique works best for isolated lymphocytes, and the isolation procedure is time-consuming making the applicability of this assay impractical for large-scale events. For G2-PCC, in comparison to DCA, there is no time saving benefit and since dicentric detection in G2-PCCs requires FISH, it is not cost effective when many samples need to be analyzed. The FISH technique also requires an additional 2 hrs for hybridization which may lead to delays in absorbed dose estimation.

The preceding account indicates that DCA will not be suitable for the first stage of triage if all the individuals in dangerous radiation zones need to be tested for exposure. In the first triage stage, the use of geographic information systems (i.e. the site of occurrence and the individuals who are at or in the vicinity of epicenter), prodromal symptoms, CBCs, lymphocyte depletion kinetics and neutrophil to lymphocyte ratio will serve better than DCA for the rapid categorization of exposed populations based on absorbed dose. This initial segregation will reduce the number of individuals who require further confirmation of absorbed dose in the second or third stages of triage, where definitive dose can be determined by biodosimetry. DCA could most certainly be applied in the second stage of triage for definitive dose estimation especially for those identified to have received > 2 Gy and < 6 Gy. This will aid in their immediate medical management and in predicting the onset and severity of ARS, specifically for those who are in the latent phase.

Cytokinesis block micronucleus assay (CBMN)

CBMN serves as an alternative to DCA for absorbed dose estimation; however, it is not specific to radiation exposure. Cytokinesis block micronucleus assay (CBMN) originally developed by Fenech and Morley (1985) is an efficient in vivo and in vitro cytogenetic tool for assessing the genotoxic effects of environmental agents. In this assay, binucleated cells after nuclear division are generated by blocking cytokinesis using Cytochalasin B. The CBMN assay measures the micronuclei (MN) originating from either broken chromosome fragments or whole chromosomes that are excluded from the mitotic spindle. Many confounding factors such as age, sex and morbidity factors can modulate the baseline frequency of MN, making the assay less reliable for estimating radiation exposures < 1 Gy. CBMN is widely used in several biodosimetry laboratories as it is easy to perform, and the absorbed radiation doses estimated by CBMN correspond well with DCA.

Like the DCA, the CBMN assay has undergone several modifications/improvements over the years to provide dose estimates in a timely manner. Some of the significant ones are the reduction of lymphocyte culturing time from 72 hrs to 48 hrs, triage mode of scoring of 200 binucleated cells, availability of automated image analysis platform(s) for MN in binucleated cells and flow cytometric detection of MN–all of these would support high throughput sample processing and analysis (McNamee et al. 2009; Shen et al. 2022; Shuryak et al. 2022; Goh et al. 2023; Lee et al. 2023; Schunck et al. 2023; Wilkins et al. 2023).

CBMN is best suited for the second and third stages of triage since the assay requires a considerable amount of culturing time (48–72 hrs) for getting enough binucleated cells. The dose detection sensitivity ranges from 1 to 4 Gy for CBMN and the upper dose limit can be increased to 10 Gy with the use of caffeine, a nonspecific inhibitor of Phosphatidylinositol 3 like kinases, that helps cells to override the cell cycle arrest imposed at G2/M phase transition (Pujol-Canadell et al. 2020). Multiparametric analysis incorporating other endpoints such as the ratio of mono and binucleate cells is being considered for the utilization of CBMN assay for high dose exposures (> 5 Gy) since lymphocytes are known to be irreversibly blocked from cell division by a radiation dependent manner thereby increasing the fraction of mononucleate cells (Repin et al. 2019). For any cytogenetic based dosimetry tool, image capture and analysis constitute the principal bottlenecks when numerous samples are to be analyzed. Recently, an automated CBMN assay known as CytoRADx has been developed for providing rapid biodosimetry (Schunck et al. 2023). To facilitate rapid analysis and dose estimation, artificial learning and machine learning approaches are being undertaken to improve the accuracy of biodosimetry (Shuryak et al. 2022).

The CBMN assay, like DCA, will be most suitable for definitive dose estimation. The long culturing time of 48–72 hrs is a potential limitation for high throughput from the second triage stage 2 facilities. Like DCA, CBMN sampling of individuals is relatively simple to perform but needs to be taken after an appropriate period following exposure. Proper storage during delivery to the laboratory, especially across national borders following a major nuclear event, is also an issue for CBMN.

Other methods

Chromosome translocations are stable aberrations that persist for several years in the peripheral blood cells of exposed individuals. However, detection of translocations involves the FISH technique using chromosome specific DNA probes which are expensive when several hundreds of samples need to be analyzed. Although translocations can be useful for retrospective biodosimetry and for predicting the long-term risk of cancer in the hematopoietic system of exposed individuals, it does not have any distinct advantages over DCA for the early phase of emergency response.

Another assay that has garnered some attention is the measurement of the phosphorylated H2AX histone (γ-H2AX) which is a surrogate marker for DNA double strand breaks (DSB). The fluorescence intensity as well as the number of γ-H2AX foci increase as a function of radiation dose making it an attractive indicator of exposure for dose estimation. However, the γ-H2AX signal reaches a peak shortly after exposure (~30 min) followed by a rapid decline within a few hours and returns to the baseline levels after about 24 hrs. This poses a major limitation of γ-H2AX as a biodosimetry marker because of the difficulty of obtaining a valid sample to analyze. However, it has been reported that the presence of γ-H2AX residual foci above baseline in ex vivo irradiated lymphocytes 48 hrs and 96 hrs after exposure is presumably due to the failure of efficient DNA DSB repair (Raavi et al. 2021). Persistence of ionizing radiation induced γ-H2AX foci was demonstrated in human primary cells up to 7 days post exposure (Vaurijoux et al. 2017). Strategies for improving the applicability of this type of assay include combining this marker with other markers for radiation exposure that appear later after exposure. One such assay is the FAST-DOSE assay that has been used to measure P53 and BAX as a function of dose in human lymphocytes (Wang et al. 2020). This type of combination of multiple endpoints could result in a high-throughput assay with a wider window of applicability for dose reconstruction during a large-scale RN event. Nevertheless, the role of γ-H2AX has still to be defined for the scenario discussed in this manuscript.

Promising omics-based biodosimetry tools for triage

Transcriptomics

Studies over the last decade on the potential use of gene expression changes for either biodosimetry or clinical outcome prediction have generated some remarkable results demonstrating the broad usability of the method in different scenarios. The equipment and the technical expertise for measuring gene expression changes in peripheral blood are available in most research and diagnostic laboratories. Some point-of-care (POC) devices are already available and more are being developed.

Different large-scale biodosimetry interlaboratory comparisons (ILCs) have proven the applicability within specialized laboratories at least for triage purposes for smaller scale events (Badie et al. 2013; Abend et al. 2023). It has been demonstrated that these techniques, when performed under optimal conditions, can estimate the absorbed dose in 4 hrs from the time of blood sampling (Polozov et al. 2019), and 1000 measurements can be achieved within 30 hrs, even in a research institute not dedicated to early high-throughput diagnostics (Port et al. 2019).

Experimental studies using the non-human primate model system revealed several advantages and limitations of the gene expression technique; see review by Port et al. (2021b). Briefly, measurements of gene expression were found to be extremely robust with modern RT-qPCR and the results are complemented by sequencing applications. However, the workflow is complex starting with a blood draw, fixation of the gene expression profile with either special chemistry or freezing techniques for RNA preservation, RNA extraction, conversion into cDNA and finally RT-qPCR measurements and therefore needs a rigid quality management system to avoid the misinterpretation of the results while doing dose estimation.

Gene expression measurements show a great potential for automation as well as for simplification and quicker dose estimates. Automation of gene expression measurements is a standard procedure in large-scale diagnostic laboratories and early publications on paper-based techniques (Lacombe et al. 2023), microfluidics or nanopore sequencing guide the way toward the development of suitable POC tools for emergency preparedness.

In summary, the techniques for gene expression measurements are available throughout the world, but specific protocols for biodosimetry need to be developed together with appropriate training and testing to establish a robust workflow and standardization of results across the laboratories. Based on current developments and several research publications, it is reasonable to state that the techniques of gene expression measurements are sufficiently developed for guiding medical decision making by confirming or ruling out significant radiation exposure and for recommending the need for more accurate biodosimetry. Currently only a few trained and experienced research groups (probably less than 20) around the globe perform gene expression techniques for either biological biodosimetry or clinical outcome prediction.

Further research developments in this area, especially on potential confounding factors, e.g. age, sex, life-style and inter-individual genetic heterogeneity (Cruz-Garcia et al. 2018); better characterization of the transcript variants (Cruz-Garcia et al. 2020), transcriptional dynamics of DNA damage response in blood (Cruz-Garcia et al. 2022); and development of field deployable high throughput POC devices are needed for effective biodosimetry and for gaining insights into a better understanding of the complex biological changes after exposure to ionizing radiation. If high throughput field deployable POC devices are developed and optimized, gene expression assays hold a great potential for use in the second stage of triage after large scale nuclear events.

MicroRNA

MicroRNAs (miRNA) are small non-coding RNA molecules that regulate genome wide gene expression. They have recently emerged as biomarkers for radiation exposure

owing to their stability in biological fluids which can be obtained in a minimally invasive manner such as blood, urine and saliva (Jacob et al. 2013; Kabacik et al. 2015; Jia and Wang 2022). Several miRNAs that are involved in DNA damage/repair (miR-34a, miR-16 and miR-21), cell death (miR150 and miR-29) and oxidative stress (miR146a and miR-223) have been found to be radiation responsive and have been utilized for radiation exposure assessment in various animal model systems (Jia and Wang 2022). Some of the miRNAs such as miR-10, miR-144 and miR-375 show radiation dose dependent expression changes making them as potential biomarkers for differentiating between low, moderate and high dose exposures. miR-150, which is abundant in the peripheral blood lymphocytes, exhibited a time and dose dependent decline in serum in mice and human cancer patients (Yadav et al. 2020). The miRNA biomarkers have been successfully utilized for predicting survival after 9 days (miR-340 and miR-452) and pleural effusion after 21 days (miR-665, MiR-324 and miR-181D) in NHPs following thoracic radiation (May et al. 2022). In addition to miRNAs, long and short non-coding RNAs (lncRNAs and sncRNAs) have been utilized as biomarkers of radiation damage (May et al. 2021). Reduced expression of lncRNA Neat1 in the lung and liver of mice after radiation indicates the potential for using lncRNAs for predicting radiation induced organ specific injuries (Hu et al. 2023). Various lncRNAs that exhibited radiation dose dependent alterations in expression levels were demonstrated in mice and human blood samples at short post exposure times (6–48 hrs), and these biomarkers can be of use for the early detection of radiation exposure assessment (Aryankalayil et al. 2018, Beer et al. 2017).

As with other omics approaches, biomarkers of miRNA, lncRNAs and sncRNAs have not been vigorously tested for various radiation exposure scenarios (radiation quality, dose, dose rate) and confounding factors (age, gender, inter-individual variability, pregenetic condition and comorbid factors). Bridging experiments between mice, NHPs and humans and then across different human ethnic populations are required for clinical validation for their use in biodosimetry. Further there is a need for developing methods for high-throughput screening to validate the miRNA, lncRNA and sncRNAs panels. Potentially, transcriptomics provides several unique tools (mRNAs, miRNAs, lncRNAs and sncRNAs) that can be used for predicting short- and long-term health risks, including the prediction of organ specific injuries. Since the assay time is relatively short (4–8 hrs), field deployable high throughput POC devices can be developed for use to rapidly evaluate exposed individuals after mass casualty incidents.

Proteomics

Altered expression levels and post-translational modifications of several radiation responsive proteins have been demonstrated to be useful for biodosimetry using in vivo mouse and NHP model systems (Becciolini et al. 1984; Hofman et al. 1990; Lee et al. 2018; Sproull et al. 2015; Zalesak-Kravec et al. 2021; Sproull et al. 2022; 2024; Tichy et al. 2024) after partial or whole-body irradiation. Radiation responsive proteins belong to various specific cell signaling pathways: DNA damage and repair response (i.e. γ-H2AX, 53 binding protein 1 [53BP1], and ataxia telangiectasia mutated protein [ATM]); oxidative stress (i.e. superoxide dismutase [SOD], Glutathione peroxidase [GPX] and heat shock proteins [HSP 27, HSP 70 and HSP 90)]); inflammatory and immune response (i.e. cytokines [interleukins IL-6, IL-8] and tumor necrosis factor [TNF α] and CRP); apoptosis and cell death markers (i.e. p53, BAX, FDXR, Caspase 3, Caspase 7); and blood based proteins (i.e. fibrinogen, serum amyloid A, and Flt-3 Ligand). These proteins can be detected in blood, urine and tissue samples for absorbed dose estimation as well as early detection of radiation sickness.

A recent in-depth review summarizes various analytical/quantitative methods for detecting radiation injury responsive protein markers and their use in determining the efficacy of medical countermeasures (Singh et al. 2023). CRP and serum amylase were the first line of protein biomarkers identified for radiation exposure, and a radiation dose dependent increase in serum amylase was reported after partial or whole-body exposure of radiotherapy patients and in the victims of Tokai-mura criticality accident (Becciolini et al. 1984; Hofmann et al. 1990; Akashi et al. 2001). Usefulness of a multiparametric approach involving cytogenetics and proteomics was demonstrated on an accidentally radiation exposed victim (Bertho et al. 2008) where Flt-3, citrulline and oxysterols were analyzed to determine the radiation effects on bone marrow aplasia, the liver, and the cardiovascular system.

An organ specific biodosimetry modeling using radiation responsive protein biomarkers was described recently (Sproull et al. 2024) which can be of potential use for radiological/nuclear mass casualty incidents. In this study, 7 predictive models were constructed based on 7000 protein analytes for organ specific injuries after total and partial body exposures in mice. The prediction accuracy for model 1 (total body irradiation and organ specific partial body exposures vs control) and model 2 (differentiation among control, total body and organ specific partial body exposures) was 92.3% and 95.4% respectively.

Recently, proteomics has greatly advanced, and the stability of some of the protein analytes offers unique opportunities to develop field deployable high throughput devices. Proteomics based biodosimetry approaches certainly have the potential to be useful in large-scale nuclear events, particularly for the second stage of triage where biodosimetry information is needed for determining the risk of ARS and perhaps in stage 3 for predicting organ specific injuries.

Metabolomics

Small molecule (<1 kDa in size) assessment through metabolomics and lipidomics has provided significant advancements in radiation biomarker discovery over the last two decades. Scenarios from total body irradiation (TBI) have provided a wealth of biomarkers that can provide classification of exposures with high sensitivity and specificity. Most studies to date have focused on animal experiments (rodents and NHPs), with limited studies on human populations due

to the complexity and ethical issues associated with such experiments; (for reviews see Coy et al. 2011; Menon et al. 2016; Pannkuk et al. 2015; Satyamitra et al. 2020; Vicente et al. 2020).

Early approaches for triage concentrated on developing methods on small portable mass spectrometry (MS) instruments, i.e. differential mobility spectrometry (DMS)-MS, that could be deployed at first or second stage triage centers (Coy et al. 2011). Small scale studies with human TBI and NHP samples showed appreciable quantitation and consistency with untargeted metabolomics (Chen et al. 2016; 2018; Vera et al. 2018). However, efforts on further developing deployable instruments for large scale radiological incidents were eventually de-emphasized, as sensitive MS instruments became more widely used in academic and clinical settings that could be used for sample processing in an emergency.

Untargeted metabolomics and lipidomics (all small metabolites detected in a biological sample without pre-selecting specific compounds of interest) have been the main driver of biomarker discovery in easily accessible samples, such as urine, blood (serum and plasma), saliva, and fecal material, within the first 7 days after exposure, as pertinent to this review. Rodent studies (mice and rats) have been the animal model extensively used in these studies, given the small size, ease of genetic manipulation, large numbers that can be included in a study, and ability to expose cohorts to a complexity of radiological scenarios. Significant attention also has been given to developing biomarkers from TBI patients treated with gamma or x-rays, neutrons, or mixed neutron and photon exposures (Tyburski et al. 2008; Lanz et al. 2009; Laiakis et al. 2014; Goudarzi et al. 2015; Mak et al. 2015; Pannkuk et al. 2016a, 2016b; Iizuka et al. 2017; Laiakis et al. 2017a, 2017b; Pannkuk et al. 2018; 2019a, 2019b, 2019c; 2022a, 2022b; Laiakis et al. 2019b; Maan et al. 2020; Sun et al. 2020a; Xi et al. 2021), i.e. exposure scenarios likely to be encountered with an IND. Most of these studies uncovered consistent perturbations in energy metabolism and specific mitochondrial intermediates, purine and pyrimidine metabolism, and tryptophan metabolism, with lipidomics revealing a generalized dyslipidemia phenotype, particularly in polyunsaturated fatty acids (PUFAs).

Some efforts have also been put forth to determine the tissue origin of these biomarkers (Golla et al. 2017) in order to pinpoint specific degrees of tissue injury. Interestingly, exposures that contained a neutron component, showed that the radiation induced changes were more prominent toward 7 days compared to 24 hours after the exposure (Laiakis et al. 2014; 2016; Golla et al. 2017; Laiakis et al. 2021), highlighting different underlying mechanisms of response to neutrons compared to photons and a delayed biological response.

While rodent studies have allowed for discovery of biosignatures with a multitude of exposure scenarios, NHP's are considered the gold standard for translation of radiation responses to human populations. Studies in urine, blood, and saliva have generally shown similar metabolic changes (Johnson et al. 2012; Pannkuk et al. 2015; 2016a, 2016b; 2021; 2022a, 2022b; 2023, Pannkuk, Fornace, et al. 2017; Pannkuk, Laiakis, Authier, et al. 2017; Pannkuk, Laiakis, Singh, et al. 2017; Laiakis et al. 2018; Kumar et al. 2020; Jun et al. 2021). Analysis of samples from TBI cancer patients undergoing hematopoietic stem cell transplantation have shown general concordance with animal studies and the potential of developing metabolomic biosignatures for biodosimetry. Urine and serum from TBI patients (Laiakis et al. 2018; 2019a) showed dysregulation of energy metabolism intermediates and fatty acid β-oxidation, in addition to imbalance of PUFAs after exposure, similarly to rodents and NHP's. Future directions should also include assessing such biosignatures in terms of confounding factors such as underlying diseases, polypharmacy, trauma, and age.

However, combining biomarkers from different 'omics' approaches may aid in eliminating such confounders and increasing the power of these 'omics' methods (Aryankalayil et al. 2023; Shuryak et al. 2023). Current efforts by multiple groups are focusing in transferring the biomarkers from the untargeted metabolomics discovery phase to a targeted approach by developing quantifiable approaches through sensitive MS instruments. Such MS instruments are found widely in clinical laboratories, academic institutions, and pharma and can be employed in an emergency in stage 2 of triage.

Neutron activation for biodosimetry

Neutron activation techniques measure radioactivity induced in biological tissues (e.g. blood, hair, nails) or metallic objects (e.g. jewelry, coins etc.) after neutron exposure. These methods are in use for decades in criticality accident management and can be applied in neutron source or beam accidents. One advantage is their specificity to neutrons, unaffected by contributions from gamma radiation. However, it requires quick measurements and knowledge of exposure time for accurate results. Activation techniques are essential for rapid dose estimation and complement individual dosimetry by providing detailed information on dose heterogeneity. Neutron activation methods have been used since the mid-1950s, with the Los Alamos criticality accident in 1956 being one notable example (Cross and Ing 1985; Delafield 1985; 1988; McLaughlin et al. 2000; Miele and Lebaron-Jacob 2008).

In the early phase of radiological accident management, sodium activation in blood is frequently used for quick triage. $^{23}Na(n,\gamma)^{24}Na$ activation (with a half-life of 14.96 hours) produces gamma emissions that are measured to estimate exposure. Measuring ^{24}Na gamma emissions using simple gamma survey instruments positioned against the abdomen is an effective way to identify exposed persons.

The induced sodium activity is primarily due to thermal neutron interactions, which affect the total activity depending on the body's exposed surface. Frontal irradiation, for example, generates more activation than lateral irradiation (which can be as low as 60%). The sodium activity also depends on body mass, with an average of 1.4 g of ^{23}Na per kg of body weight. Sodium activity does not directly correlate with exposure severity due to dependence on neutron fluence energy, i.e. fast neutrons generate less activated sodium but result in a higher dose. Therefore, accurate dose

estimation requires knowledge of the neutron spectrum, orientation, and gamma-to-neutron dose ratio. Whole-body counters or blood gamma spectrometry provide more precise sodium activity measurements, with whole-body counting offering the lowest detection limits (a few tens of μGy for thermal neutron doses) (Cross and Ing 1985; Miele and Lebaron-Jacob 2008).

Apart from sodium activation, sulfur activation in hair, nails, and wool is another useful method for dose reconstruction. The $^{32}S(n,p)^{32}P$ reaction, with a threshold of 3 MeV and a half-life of 14.28 days, is a clear indicator of fast neutron exposure. Since the cross-sections remain constant between 3 and 20 MeV, sulfur activity is proportional to neutron tissue kerma. Hair sampling from different parts of the body provides insights into dose distribution and victim orientation. Measuring ^{32}P activity requires chemical sample preparation and detection using Geiger-Müller counters, proportional counters, or liquid scintillation techniques. The detection limit is about 0.05 Gy for 1 mg of hair, and the total neutron dose can be estimated using a coefficient of 1.23 Gy per Bq of ^{32}P per gram of hair (IAEA 1982; Lebaron-Jacobs et al. 2007).

These techniques have been used since mid-1950s, using IAEA established protocols (IAEA 1982). Regular training exercises ensure technical proficiency, with inter-laboratory comparisons documented in several reports (Médioni and Delafield 1997; Médioni et al. 2004).

Electron paramagnetic resonance (EPR) spectroscopy for biodosimetry

The basis of EPR biodosimetry

EPR detects paramagnetic species (such as point defects and free radicals) including those induced by ionizing radiation, using a combination of static and oscillating magnetic and electromagnetic (EM) fields. The intensity of the EPR spectra, which quantify the radicals formed in materials after irradiation, can then be related to the absorbed dose using a calibrated linear response curve. While EPR can be used on many different types of materials such as calcified and keratinized biological materials mineral glass, polymers, sugars and cotton (ICRU report No. 94, 2019, Trompier et al. 2009), the focus here is only on those that appear applicable for use in large-scale radiation events, i.e. using the ex vivo measurements of teeth based on tooth biopsies, in vivo teeth, and in vivo nails. These are based on the stability of the radiation-induced EPR signals are hydroxyapatite in teeth materials and keratin in nails. The radiation-induced radicals in these materials are relatively stable after hours of post exposure and persist for a very long time (e.g. millions of years for enamel and days to weeks for keratin). Bone is another material with stable radiation-induced radicals but is not discussed here because sampling is invasive and not suitable for this scenario.

Because these EPR materials, particularly hydroxyapatite, have negligible amounts of hydrogen, neutrons do not induce a measurable response. Thus, EPR can detect gamma rays that are proportionate to the absorbed dose but essentially ignores the presence of neutrons (Zdravkova et al. 2003). This can be a virtue when combined with biodosimeters that respond to neutrons, but a limitation when using EPR alone in potential mixed fields. EPR biodosimetry acts essentially as an inert dosimeter that is unaffected by prior or concomitant physiological or pathophysiological factors. This contrasts with biologically based biodosimetry techniques described earlier, which respond directly or indirectly to radiation exposure and whose magnitude can be impacted by the overall dynamics of the cellular radio response. However, when paired appropriately for the population at risk, EPR biodosimetry can complement other methods (e.g. blood analyses, cytogenetics) thereby together providing a comprehensive exposure assessment (Clairand et al. 2008; McKeever and Sholom 2016 IAEA, 2018; ICRU, 2019).

The EPR measured effect on the material is cumulative over time and is not impacted by dose rate. Moreover, EPR signal intensity directly correlates with the absorbed radiation dose at the exposure site, offering a cumulative, site-specific measure. This could be useful for assessing the cumulative effect of fallout over time and for assessing whether the dose was sufficiently heterogeneous to spare enough bone marrow so that the victim can recover without needing extreme measures such as a bone marrow transplant.

The actual measurement process and analysis are both nondestructive, allowing for the possibility of making multiple and repeated measurements. Measurements can be performed immediately after the exposure (i.e. as soon as it would be feasible to measure victims after a nuclear event), and they would provide stable estimates for the entire time enabling the feasibility to perform triage, and dose estimates for informing ARS treatment.

There are several additional features that make in vivo EPR spectroscopy ideal for use in triage stage 2. In vivo EPR 'sampling' for both teeth and nails is completely noninvasive, requiring only that the head (for teeth) or limbs (for nails) be held stationary within a non-significant-risk magnet and resonator for ~5 minutes of measurement and analysis time. Sample preparation for in vivo teeth is not needed; preparation for nails (e.g. cleaning) is extremely rapid (within 5 minutes) and requires minimal consumable resources. For both approaches, measurements including their analysis are fast (<5 minutes) and available immediately at POC for triage decision-makers.

Ex vivo tooth measurements would need to be performed at a specialized laboratory offsite. The sampling, as for most biologically based techniques, needs to be done at the site where victims are gathered. The mini biopsies (2–5 mg) are minimally invasive and could be performed within 5 minutes by non-experts with minimal training and few consumable resources (Romanyukha et al. 2014a; IAEA, 2018). No sample preparation is required; packaging samples for transportation would not require temperature control or other special protection (other than not being exposed to additional radiation during shipment).

EPR measurements of teeth

In vivo *tooth measurements.* EPR spectrometers working in L-band (1.2 GHz) enable in situ enamel measurements. The

L-band approach, compared to using higher frequency bands, has minimal heat transfer (which is important for in vivo measurements made in teeth; even though hydroxyapatite is inert, teeth have living components and tissues in the mouth and head are within the EM). L-band, however, has the disadvantage of being less sensitive for estimating dose (Miyake et al. 2000; Iwasaki et al. 2005).

L-band biodosimetry typically measures the central upper incisors, as they are easily accessible and less likely to have fillings. Advanced prototypes can provide triage-level results (< 2 Gy) within 5 minutes (Williams et al. 2014; Flood et al. 2016). Transportable equipment has been successfully deployed in real-world scenarios, such as Fukushima-Daiichi (Miyake et al. 2016; Yamaguchi et al. 2021). Validation studies confirm accuracy also in patients undergoing total or partial irradiation (Williams et al. 2011; Yamaguchi et al. 2023; Draeger et al. 2024). However, regulatory clearance (e.g. FDA) is still pending.

Challenges for L-band include background signals from ultraviolet (UV) exposure, enamel variations and impurities, and poor signal-to-noise ratios (SNR) caused by movement or resonator slippage (Fattibene and Callens 2010; Williams et al. 2014; Yamaguchi et al. 2016; Umakoshi et al. 2017; Khailov et al. 2020; Nakai et al. 2022; Oh et al. 2024). Solutions include improved magnets, wireless resonators, and motion compensation systems (Flood et al. 2016; Schreiber et al. 2016; Koo et al. 2023; Oh et al. 2024).

Despite portability and rapid measurement capability, scaling up remains challenging. To measure the thousands or more in a large-scale event, even at a second stage of triage, many EPR devices would need to be deployed to various sites in the field (e.g. 625 devices to measure 1 million victims in a week).

Ex vivo *EPR tooth biodosimetry*

For the 2nd stage triage, tooth enamel mini biopsies can be analyzed at higher frequencies (Q band, i.e. 31–50 GHz). The higher sensitivity of the higher frequency provides sufficient sensitivity for a sample mass of a few mg. While effective for definitive dose assessments, ex vivo EPR biodosimetry requires expensive equipment, skilled operators, and is not field deployable (Romanyukha et al. 2007, 2014a). Hence, samples would need to be transported from the incident site(s) to existing centers with the equipment. Q-band EPR has been successfully used for ex vivo tooth biodosimetry in several cases of management of radiological accidents since 2011 (ICRU report No. 94, 2019; IAEA, 2018), and ex vivo techniques were positively evaluated in a French national crisis exercise in 2024.

Q-band EPR on enamel biopsies has several advantages. It does not require technical development (spectrometers are commercially available), and the technique is already operational. Nevertheless, it will be necessary to develop the operational and organizational aspects of taking and transporting enamel samples from the event site. Even if, with the few machines already available, the capacity to rapidly measure a large number of samples is already high with the availability of a few machines compared with those of other biodosimetry methods. An operational network of laboratories with Q-band instruments will need to be developed at an international level to increase the measurement capacity, with sufficient training and development of protocols to ensure a high level of reliability and standardization.

EPR biodosimetry of nails

In vitro *nail biodosimetry using nail clippings.* Using nail clippings for radiation dose assessment was initially viewed as a very promising technique due to its noninvasive self-sampling and use of high-frequency EPR with its greater sensitivity (Trompier et al. 2007; 2009; He et al. 2011; Romanyukha et al. 2011; Trompier et al. 2014a; Marciniak and Ciesielski 2016). However, artifactual signals from mechanical clipping, nail drying, exposure to oxygen or water and polish use reduced its reliability. Concerns about the stability of the radiation induced signal and separating it from the background further eroded interest in this approach. Nevertheless, procedures were proposed to consider all the signal complexity and ex vivo nails EPR dosimetry was successfully used in a few radiological accident cases (IAEA, 2018, Trompier et al. 2014b, Romanyukha et al. 2014b). Owing to complexities in the proposed procedures for nail dosimetry technique, this method is not currently considered as viable for large-scale events until further developments to resolve the technical issues.

In vivo *nail dosimetry*

In vivo EPR methods for nails avoid the need for clippings but require higher frequency (X-band) resonators to improve sensitivity (He et al. 2011; Swartz et al. 2012). Advanced resonators, such as dielectric-backed aperture and surface array designs, enhance dose measurement by focusing the EM fields on the nail while minimizing interference from the nailbed (Sidabras et al. 2014; Grinberg et al. 2016; Guo et al. 2021a, 2021b; Flood et al. 2023). These systems have achieved proof-of-concept level sensitivities sufficient for triage and retrospective dosimetry but still require further advanced developments, including refinements for stability during measurement and ergonomic improvements.

Planned innovations, such as multi-limb simultaneous assessments, could reduce measurement times to under 5 minutes. Despite progress, in vivo nail dosimetry currently requires sophisticated equipment and expertise, limiting its scalability for large-scale events and precluding its use at POC locations. It may be especially suitable for targeted victims, such as those with combined injuries, where accurate assessments are critical for medical decisions at later stages of triage and dose estimation for ARS care decision-making.

The ability of nail biodosimetry to query multiple limbs with independent dose assessments (i.e. up to four specific sites) provides an advantage in determining whether the dose was sufficiently heterogeneous to spare enough bone marrow. This information would provide useful guidance to allow medical personnel to avoid using hematopoietic treatments, making it valuable for victims with potentially heterogeneous exposures.

This feature could reduce the need for medical interventions by confirming lower radiation doses in critical areas.

Collectively, EPR biodosimetry could have a major positive impact on 2nd stage triage and to lesser extent in 3rd triage stage. In triage stage 3, victims with concomitant injuries, burns and severe stress which would impact biologically based biodosimetry, EPR biodosimetry could help determine the degree of risk with combined injury. Research has been conducted on both in vivo tooth and ex vivo tooth biopsies to ensure quality of the measurements. L-band in vivo EPR tooth dosimetry is at the stage where it could seek regulatory approval as a medical device. In vivo nail biodosimetry, however, it still needs development before assessing its suitability.

Inter-laboratory comparisons and field studies of EPR biodosimetry are also important for preparedness. To date in vivo tooth biodosimetry has not been included in inter-laboratory or small field tests, while ex vivo tooth biopsies have had some inter-laboratory application in supporting medical management of accidentally irradiated individuals. In vivo nail techniques are not fully developed to warrant inter-laboratory comparisons and field studies.

Summary

Successful response to large-scale radiological/nuclear incidents requires the coordinated integration of three important networks: the emergency response network, biodosimetry network, and medical management network (Figure 1). Given the complexity of exposure scenarios that may involve single or mixed radiation with different doses, dose rates and modes of exposure (internal and external exposure/contamination), a single biodosimetry tool is probably not sufficient for mass casualty scenarios. Further, current cytogenetics and omics-based biodosimetry tools as well as EPR have different levels of sensitivity and specificity for absorbed dose estimation, necessitating the need for a multi-parametric approach for different stages of triage as discussed in this review. A few studies have utilized the multi-parametric approach using combinations of different biodosimetry assays such as prodromal symptoms, hematological assays, DCA, translocations, CBMN, gene expression and γ-H2AX (Bertho et al. 2008; Ainsbury *et al.* 2014; Grégoire et al. 2013; Zeegers *et al.* 2017; Tichy *et al.* 2018) for triage applications. A multi-parametric biodosimetry approach that combines the traditional and emerging methods will maximize their utilities in large-scale emergencies.

Examining the techniques in the context of a large-scale nuclear event requires considering all facets of logistics, including obtaining and shipping valid samples, speeding up analysis and eliminating roadblocks, combining laboratories and repurposing readily available instruments and experts, and communicating the results to decision makers for timely triage and treatment. These logistical considerations are seldom featured in research evaluations of biodosimetry techniques but are important criteria for planning their appropriate use in real scenarios.

Developments of deployable devices as well as high throughput automated biodosimetry platforms are essential to adequately respond to radiological/nuclear emergencies. Most importantly, a robust infrastructure with equipped biodosimetry laboratories and trained personnel is an absolute requirement and this has been achieved in many countries and continents by forming viable biodosimetry networks for responding to radiological/nuclear emergencies. Investment is needed for training and maintaining the pool of biodosimetrists/radiation biology specialists for pre-event readiness preparation in collaboration with emergency response and medical management networks.

As others have noted, biodosimetry tools/devices should be integrated into local, state, regional and national emergency medical response frameworks as well as with the national disaster management plans. Additional considerations include ethical challenges, equitable distribution of resources as well as logistical planning for sample collection, transport, and inter-laboratory coordination for biodosimetry assessment. Organizing periodic simulated exercises and drills for different types of nuclear exposure scenarios at the state, regional and/or national levels will not only lead to better knowledge and strategies for responding to such mass casualty events but also increase awareness of the need for further development of suitable biodosimetry techniques that are better suited to address ever existing inherent logistical problems associated with such events.

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