Radiological and Nuclear Countermeasures Program

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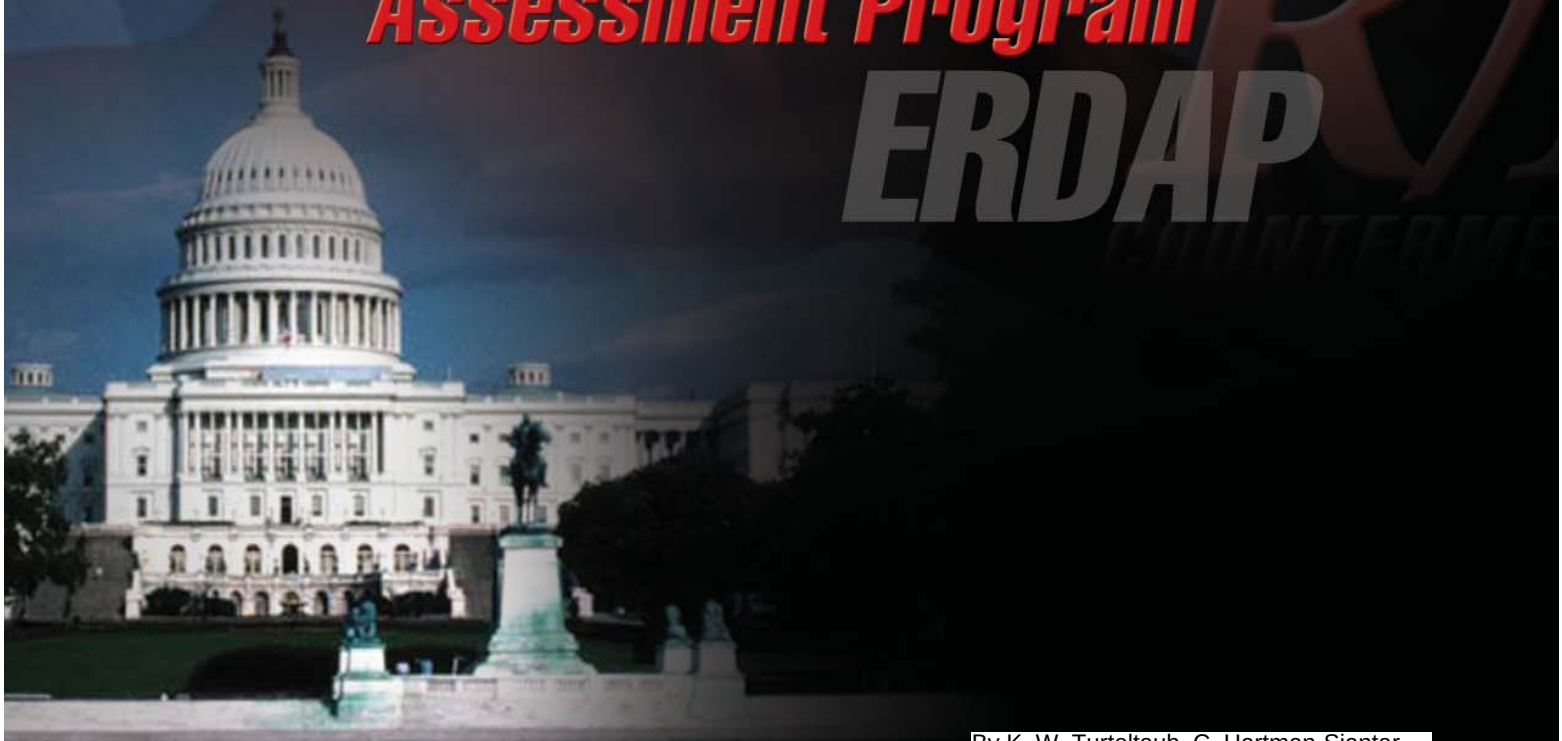
UCRL-TR-215887

Technology Assessment and Roadmap for the Emergency Radiation Dose Assessment Program

ERDAP



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Department of Homeland Security

Technology Assessment and Roadmap for the Emergency Radiation Dose Assessment Program ERDAP

This work was performed under the auspices of the U.S. Department of Energy by the University of California, Lawrence Livermore National Laboratory under Contract No. W-7405-Eng-48.

June 2005

UCRL-TR-215887

Lawrence Livermore National Laboratory

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Executive Summary

A Joint Interagency Working Group (JIWG) under the auspices of the Department of Homeland Security Office of Research and Development conducted a technology assessment of emergency radiological dose assessment capabilities as part of the overall need for rapid emergency medical response in the event of a radiological terrorist event in the United States. The goal of the evaluation is to identify gaps and recommend general research and development needs to better prepare the Country for mitigating the effects of such an event. Given the capabilities and roles for responding to a radiological event extend across many agencies, a consensus of gaps and suggested development plans was a major goal of this evaluation and road-mapping effort. The working group consisted of experts representing the Departments of Homeland Security, Health and Human Services (Centers for Disease Control and the National Institutes of Health), Food and Drug Administration, Department of Defense and the Department of Energy's National Laboratories (see appendix A for participants).

The specific goals of this Technology Assessment and Roadmap were to:

- Describe the general context for deployment of emergency radiation dose assessment tools following terrorist use of a radiological or nuclear device
- Assess current and emerging dose assessment technologies
- Put forward a consensus high-level technology roadmap for interagency research and development in this area.

Below we provide a summary of the consensus of needs, gaps and recommendations for a research program in the area of radiation dosimetry for early response, followed by a summary of the technologies available and on the near-term horizon. We then present a roadmap for a research program to bring present and emerging near-term technologies to bear on the gaps in radiation dose assessment and triage. Finally we present detailed supporting discussion on the nature of the threats we considered, the status of technology today, promising emerging technologies and references for further reading.

Needs Evaluation

In the event of a terrorist-driven radiological event, emergency radiation dose assessment by first responders will be necessary to identify and focus the use of precious medical resources. Terrorist-driven exposure to radiation can result from several forms of radiological or nuclear devices (R/N), ranging from non-explosive, and clandestine exposure to a radiation source, to explosively-driven radiological dispersion devices (RDD), and even improvised or stolen nuclear weapons (IND). Incidents may result in external exposure (radiation dose, without the presence of radioisotope(s) in or on the body) and/or the uptake of radioactive materials by inhalation, ingestion, skin absorption, wound contamination or injection of radioisotope(s) as embedded material. In many instances, emergency response personnel are the first medical responders to contact victims. In other cases, the medical treatment facility itself serves as the "first response" center. In both cases rapid evaluation of patients is key to early initiation of medical intervention and ultimately to saving lives.

Tools to rapidly triage individuals needing medical attention and to intelligently direct medical treatment to those needing immediate care will optimize the use of scarce resources, improve survival, and enhance public confidence in government. It is imperative that victims who have been exposed to significant levels of radiation following a terrorist event, especially one involving an IND or stolen nuclear weapon, be identified and sorted from those that are concerned that they have been exposed, but who have received no or a non-health threatening radiological dose as rapidly as possible so that treatment can be administered to those in need. This is no small task as it is expected that for every person requiring medical attention, 100 – 500 persons concerned about their possible exposure will request medical evaluation, thus taking up precious time and resources. The more rapidly this can be carried out the faster precious medical resources can be focused on those in need of medical intervention.

Radiation dose assessment is critically important because medical treatment depends on understanding the dose an individual receives. Currently, medical intervention depends on the patient's medical signs and symptoms resulting from the radiation dose received which, in turn, depend on distance from the initial event and exposure to fallout. Immediate treatment is needed for otherwise healthy persons who have had whole or near-total body radiation exposure exceeding 2 Gy. 3.5-4.5 Gy exposure, without treatment, would result in at least 50% mortality within 3 to 6 weeks. Combined injury (radiation and burn/blast trauma) lowers the threshold for treatment to approximately 2 Gy. In addition to the clinically significant doses that could be received, with some radiological scenarios such as an RDD or "dirty bomb," many victims may have severe levels of internal contamination from inhalation of the radionuclide(s) dispersed by the bomb. Current medical guidance recommends that treatments for internal contamination should begin within hours of exposure (Ceverny, 1989).

Patients with very high radiation doses or significant internal contamination will likely present with no clinical symptoms other than possible conventional trauma. In most cases radiation sickness takes days to weeks to present clinical manifestation. The severity of the resulting lesions and time of onset depends, in part, on the delivered dose and how soon interventions are begun. Medical management and decisions regarding initiation of simple interventions such as removal of contaminated clothing and washing of the body; early initiation of more

aggressive therapies such as chelators for reducing internalized radionuclide dose, cytokines for reducing the effects of bone marrow suppression and others depend on knowledge of expected clinical responses. Clinical response is correlated with acute radiological dose. Current state-of-the-art practice for determining acute radiation doses relies on three methods:

1. Time-to-onset and severity of nausea and vomiting
2. Lymphocyte depletion kinetics
3. Chromosome aberration cytogenetics.

Presently available methods are not satisfactory for managing the medical casualties from and R/N event and there is urgent need to develop new capabilities to assess radiation dose. Assessment of emesis is only a rough indicator of acute exposure and can never be relied upon alone, especially for quantitative information. Lymphocyte depletion provides direct quantitative information but requires analyzing peripheral blood samples from the patient over a period of 12 hours to 7 days, while chromosome aberration analysis requires a qualified cytogenetic laboratory and 48 to 72 hours to analyze after sample receipt. Because none of these methodologies alone are reasonably satisfactory for managing mass casualties from a large RDD or an IND event in the first few hours, there is an urgent need to develop novel emerging technologies to supplement the current capabilities for assessing emergency radiation doses.

Technology Gap

Within the first 72 hours tools are needed that can detect whole body doses of between 1–8 Gy and can run at a rate of 1 assay every 5 minutes. These tools presently do not exist.

Based on radiological and nuclear weapons scenarios that range from clandestine sources to full-scale nuclear weapons, combined with decision-point dose levels recommended by current medical consensus on triage and treatment, the following throughput, turnaround time, sensitivity, and range are used as generally ideal reference points for emergency-response dose assessment tools:

- Hand-held diagnostic device with throughput of 1 assay per 5 minutes or less
- Field-laboratory turnaround time of 24 hours or less
- Hand held field laboratory and reference laboratory radiation dose assessment systems need a detection range 1–8 Gy, with thresholds at 1.5 and 4.5 for triage and 2-3 and 6-7 for treatment decisions for hand-held, field laboratory, and reference laboratory diagnostic dose assessment system.
- Critical need to identify those who do not need immediate medical attention

Recommendations and Priorities

A research and development program focused on providing simple tools that can provide an estimate of whole or near whole body radiation dose is needed which can discriminate approximately 2 Gy and 4 Gy exposures from background and can provide throughput of 1 assay per 5 minutes. A process leading to fielding such devices is possible within the next 5 years. The goals of this program should be to:

Clarify device needs and requirements

- Combine user input, technology assessment and operations/systems studies to guide development of realistic requirements and appropriate system architectures for radiation dose assessment tools.
- Focus initial studies on defining the role of pre-positioned dosimeters, optimizing the size and organization of a national cytogenetics network, and estimating the added value of dosimetry technologies still on the horizon, such as luminescence, ultrasound, and molecular markers of radiation dose and injury. Prioritize investment based on user input, available technology capabilities and operational needs developed under the first bullet.
- Develop a clear set of decision points to determine whether individual technologies are on track to be deployed, and define a path/mechanism for deployment.

Maximize use of existing technologies

- Concentrate near-term technology investments in developing pre-positioned dosimeter concepts and establishing a stable U.S. cytogenetics capability for use in the event of an R/N incident, in line with the results of systems studies to assess their relative value in saving lives for realistic radiological or nuclear events.

Pursue longer-range research and development to fill gaps with existing technologies

- Answer key questions about the throughput, specificity, prognostic value, sensitivity, range, accuracy and reliability (including person-to-person variability and impact of confounding factors) for new radiation dose and injury assessment technologies.

Conduct a demonstration program to assess the value of existing and proposed technologies

- Conduct field tests and leverage already-scheduled events to assess systems-study assumptions, new-device performance, and con-ops in an operational environment.

Technology Summary

Technology Assessment

Table 1 summarizes what we know and don't know about current and emerging technology for emergency dose assessment and triage. Overall, the prospects of current technologies meeting emergency-tool assessment criteria are limited:

- Direct measurement of external radioactive emissions on body surfaces and clothing is a standard tool for first responders. High throughput screening for qualitatively detecting overt contamination is possible with portable probes for many isotopes. This technology is viewed as an important tool by first responders for triage decision making in the first hours following a detonation, primarily for use in decontamination decisions. Early external decontamination removal is important to reducing whole body radiation dose. However, it only provides an estimate of the dose received from external contamination on the clothing and body at the time of measurement and this dose may be a small component of the total dose received by the victim, depending on the type of weapon used.
- Direct measurement of radioactive emissions *in vivo* is a practical solution for measurement of internal radioactive contamination; however high-throughput sample-processing systems and quick-reference guidance for converting contamination measurements do not exist. These technologies are important to long-term case management and could be useful for early initiation of relevant therapies.
- Pre-positioned dosimeters generally perform well for dose assessment criteria; the most cost-effective and easy-to-read candidate, the SIRAD card, currently has limited distribution with a shelf-life reported to be one-year when stored properly.
- Conventional cytogenetic assays are presently considered the standard for estimating whole body biological dose. Such assays have demonstrated capability to estimate doses below 1 Gy in a controlled laboratory setting. However, use of cytogenetics in a triage situation is difficult below 1 Gy, and standard assays take 48-72 hours to complete. Shorter-turn around (24 hours) assays are not yet well benchmarked or available.
- Lymphocyte depletion is not detectable following radiation doses of less than 5 Gy within the first 24 hours, and lymphocyte kinetics which require serial measurements of 3 or more counts, exhibits a dose threshold near 1 Gy but likely will be logistically difficult to obtain within this time period after a mass casualty incident without development of hand-held blood counter device.
- Dose assessment based on time-to-vomiting, has variable sensitivity with only 35% of victims vomiting after a 2 Gy exposure and >90% incidence following 6 Gy exposure; dose assessment based solely on use of prodromal symptoms including time-to-vomiting will likely exhibit significant false positives.

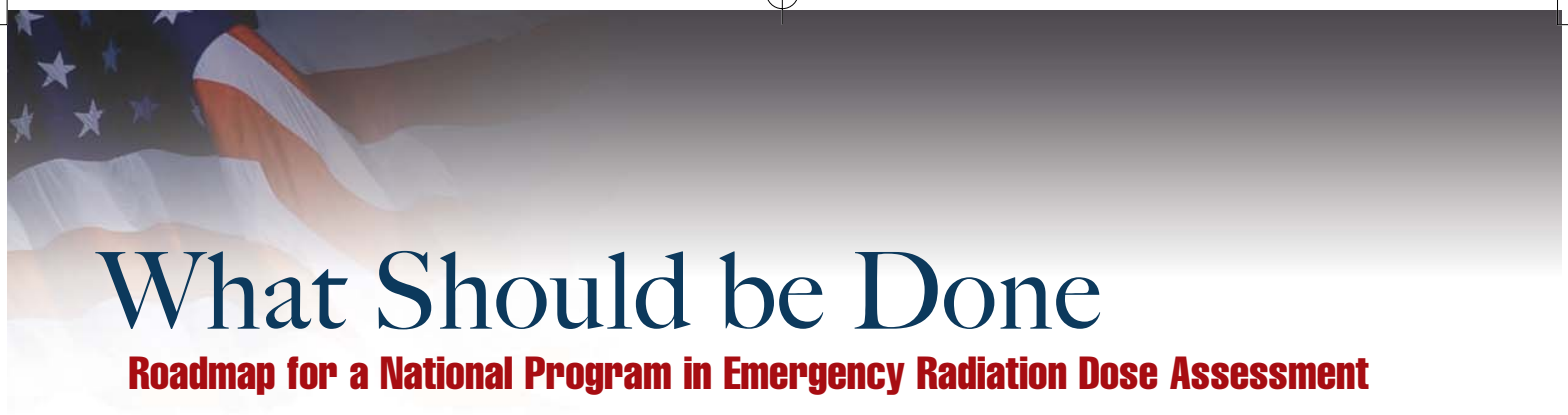
Emerging technologies offer potentially significant advantages, but present substantial uncertainties that must be resolved:

- Molecular biomarkers, including mRNA and proteins, offer a new set of tools for hospital-based, fieldable, or even self-administered radiation dose assessment. However, research is necessary to assess person-to-person variability and impact of confounding factors such as stress, gender, and age among others. Prototype devices must demonstrate sensitivity (as well as cost, size/weight, and ruggedness) in realistic test scenarios.
- Luminescence, particularly Optically Stimulated Luminescence (OSL) and Electron Paramagnetic Resonance (EPR-ESR) are technologies that can provide the potential for measurement of radiation doses *in vivo* at or below the 1.5 Gy thresholds in human tissues. Sensitivity and inter-individual variations must be demonstrated experimentally. Prototype devices must be built and tested for cost, size/weight, performance, and ruggedness.
- Ultrasound is a particularly exciting opportunity for assessing tissue damage from radiation and may have much broader applications. Sensitivity, as well as person-to-person variation is not known. Operability in the field has not been demonstrated and fieldable hospital-based prototypes require development and evaluation.
- Fortuitous dosimeters promise simple, accurate dose estimates from common objects that may be at or near the victim(s), using luminescence as the primary approach for readout. However the value of relying on fortuitous objects which may or may not be available, in an emergency setting needs to be demonstrated. Accuracy and sensitivity, cost, size/weight, performance, and ruggedness are presently unknown. Con-ops are not developed.
- Hand-held devices for blood cell counting, breath-gas analysis, and medical recording, tagging of casualties, and triage tools should be explored and could be an essential part of the response system. The utility of these tools and how best to use them are somewhat undefined. Current recording criteria identified for emergency tools should be expanded to include plume/position-based dose estimates as well as newer dosimetry tools as they become available.

Even if technologies do not meet operational requirements, they may still have useful applications in response to a radiological or nuclear event. An example of this is cytogenetics, the gold standard for biodosimetry: even though likely throughputs and turnaround times do not match the needs described above, cytogenetics will no doubt prove invaluable in directing treatment for those already identified for as in need.

Table 1. Summary of what we know and don't know about current and emerging dosimetry technologies.

	What we know	What we don't know
Current Methods and Tools		
Measurement of radioisotope contamination	Many available handheld detectors for external assessment. Internationally accepted guidelines for radiation dose estimation. Available instrumentation for body fluid analysis, limited high-throughput capability.	Radiation dose estimation models need more attention, and may have significant inaccuracies, especially for sub-populations.
Biological and clinical signatures of radiation dose	Lymphocyte depletion is not detectable in the first 24 hours for less than 5 Gy. Lymphocyte kinetics will be logistically difficult to obtain within this time period and vary significantly from individual to individual. Time-to-vomiting is limited in sensitivity (only 35% of victims vomit with a 2 Gy exposure) and is widely variable from individual to individual. Conventional/cytogenetic chromosome aberration assessment (scoring 1000 metaphase spreads) takes 48-72 hours and has demonstrated capability to estimate doses from 0.20 to 6.0 Gy (acute photon equivalent dose), while cytogenetic triage (scoring 40-50 metaphase spreads) becomes difficult below 1 Gy. The current U.S. cytogenetics capability is limited to less than 500 standard assessments over a 2-week period. These methods may not accurately predict partial-body or organ-specific exposure.	Effect of dose rate on lymphocyte counts or depletion rate is not known. Psychosomatic impact on time-to-vomiting is not established for a mass casualty situation. Shorter-turnaround (24 hour) cytogenetic chromosome aberrations are not yet well benchmarked.
Pre-positioned physical dosimeters	Current technology meets dose threshold and dynamic range requirements. May not accurately predict partial-body or organ-specific exposure.	Shelf-life, longevity not well established for SIRAD cards. Social and medical questions about how to interpret "significant radiation exposure" readings and false positives.
Emerging Technologies		
Physical changes in human tissues	OSL and EPR could enable accurate and safe estimation of dose from non-invasive *in vivo* measurements in teeth, with a threshold at or below 1.5 Gy. Ultrasound may provide evidence of local radiation injury around wounds. Potential for turnaround and throughput in 1 min / assay timeframe.	OSL sensitivity significantly below 15 Gy is anticipated from theoretical arguments, but has not yet been established experimentally. *In vivo* EPR dosimetry sensitivity and potential inter-individual variation effects are unknown. OSL and EPR field equipment (portable, etc.) has not been demonstrated. Dose sensitivity of ultrasound is not established.
Personal items and other fortuitous dosimeters	Several materials have been demonstrated to provide very accurate dosimetry, with a detection threshold well below 1.5 Gy. Potential for turnaround and throughput in 5 min / assay timeframe. Hard to depend on this approach for all victims, since dosimetry materials are fortuitous. May not accurately predict partial-body or organ-specific exposure.	Con-ops and instrumentation for widespread use have not been established.
Biological markers	Several mRNA and protein candidates demonstrated to be dose dependent, with sensitivity well below the 1.5 Gy action threshold. Hand-held devices for blood cell counting, breath gases analysis, and triage medical recording involving the tagging of casualties will assist with triage. Instrumentation concepts (protein and PCR assays) have been demonstrated for other applications, and could provide 5 min turnaround and throughput and / or be run in a highly multiplexed format. Potential for a self-administered disposable format for proteins. May not accurately predict partial-body or organ-specific exposure – this could be addressed with significant further research.	Time dependence and variation with confounding factors such as age, stress, and health status have not been well established. Instrumentation throughput, ruggedness, accuracy and sensitivity have not been established for this application. Organ–specific markers have not been established. Utility of other biological markers such as metabolites need investigation. Ability of markers to detect/differentiate whole or partial body exposures are unknown.



What Should be Done

Roadmap for a National Program in Emergency Radiation Dose Assessment

Table 2 lays out a roadmap and a set of deliverables for a National Program in Emergency Radiation Dose Assessment. We advocate the development of a cooperative, interagency program to efficiently develop capabilities, both near and far-term, that could have a major impact on the management of victims and the potentially exposed individuals in the aftermath of the detonation of an RDD or IND. We focus on what will be needed within the first 72 hours following an event to determine who will be in need of follow-up care or medical surveillance. This proposed program has four major goals:

1. Clarify device needs and requirements
2. Maximize use of existing technologies
3. Pursue longer-range research and development to fill gaps with existing technologies
4. Conduct a demonstration program to assess the value of existing and proposed technologies and optimize their development for fielding and commercialization.

Below is a brief discussion of priority investments for each of these goals.

Clarify device needs and requirements.

The expected user community should be polled to determine the needs and requirements for the technology to be used in deployments. The requirements developed should be device and application specific. Many factors must be considered in the choice and design of this technology including:

- Desired throughput.
- Specificity.
- Ease of use (level of training required to operate the equipment).
- Sensitivity.
- Time to complete the assays.
- Result integration for end-user application
- Allowable false positive/negative rates.
- Sample matrices/ease of sample collection and processing.
- Shelf life.
- Costs (manufacturing/use).

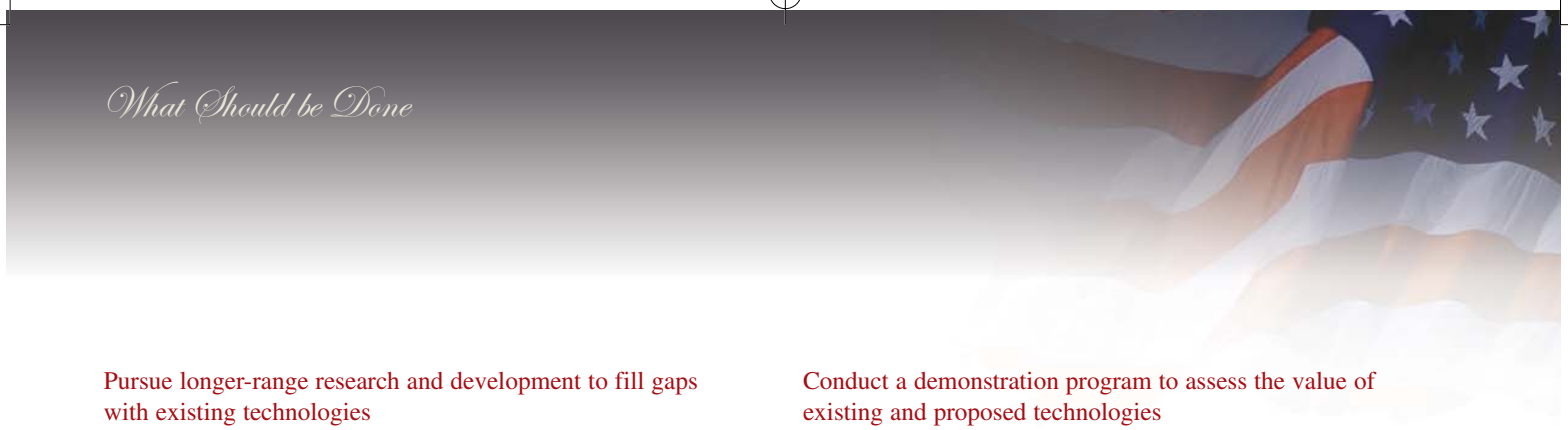
The requirements may differ depending on the intended use of the devices. For example field triage devices may have a different set of requirements for cost and ease-of-use than devices used in clinical settings. The exact scenarios of use and expectations must be determined.

User input and technology assessment should be used to inform quantitative operations/systems studies to guide con-ops and medical response architecture development and help prioritize science and technology investments. The initial focus should be on:

- Optimizing the size and organization of a national cytogenetics network with each reference laboratory supplemented by satellite scoring laboratories capable of each analyzing 500 samples per week.
- Defining the role of pre-positioned dosimeters
- Estimating the added value of radiation injury and dose assessment technologies still on the horizon, such as luminescence, electron paramagnetic resonance, ultrasound, molecular markers of radiation dose, and hand-held devices for bioassay (blood cell counting, breath gases, etc.) measurements and recording/tagging of individuals.
- Developing a clear set of decision points and critical development paths to determine whether individual technologies are on track to be deployed, and define a path/mechanism for deployment.

Maximize use of existing technologies

Near-term technology investments should be concentrated on stabilizing a U.S. cytogenetics capability and developing pre-positioned dosimeter concepts, in line with the results of systems studies to assess their relative value in saving lives for realistic radiological or nuclear events. A deployable hematology capability should be investigated as an available resource, following the IAEA ERNET model, to provide the ability to supplement local capabilities for serial blood cell counts on suspected radiation casualties. Radioisotope contamination assessment laboratories should be equipped with high-throughput sample-assessment systems based on existing commercial-off-the shelf (COS) technologies.



What Should be Done

Pursue longer-range research and development to fill gaps with existing technologies

Longer-range research and development should be conducted on emerging dosimetry technologies to answer key questions about the specificity, prognostic value, throughput, sensitivity, range, accuracy and reliability (including person-to-person variability and impact of confounding factors). A variety of technologies are presently in the marketplace for diagnosis of a number of diseases. Some of these technologies may be useful for radiation dose assessment with minimal development. Evaluation of potentially useful technologies should be carried out and emphasis placed on their conversion for use in radiation dose assessment.

Conduct a demonstration program to assess the value of existing and proposed technologies

Finally, field tests, conducted as stand-alone studies as well as piggy-back exercises attached to already-scheduled events, should be done to assess operational assumptions, new-device performance, and con-ops in an operational environment.

Table 2 summarizes a high level, 5-year roadmap to accomplish these goals.

Table 2. Suggested Goals for National Program in Radiation Assessment

	1 year	1 to 3 years	3 to 5 years
Systems analysis to clarify device needs and requirements	Analyze scenario for one radiological and one nuclear incident type. Define relative roles of physical and bio-dosimetry, perform cost-benefit analyses for dosimetric systems.	Provide initial estimate of operational device requirements for R/N scenario's for physical and bio-dosimetry tools. Evaluate hospital instruments and technicians to determine capability to perform required measurements.	Refine estimates based on progress in laboratory experiments and initial field demonstrations. Work with instrument manufacturers to modify hospital-based instruments to be capable of measuring threat isotopes, and provide training to technicians.
	Determine optimum size and organization of a national cytogenetics network. Evaluate competing technologies and define the most effective role of pre-positioned dosimeters. Develop criteria to distinguish the added value of emerging dosimetry technologies. Evaluate and compare competing technologies to select the best available.		
Short-range efforts to maximize use of existing technologies	Define a blueprint to stabilize a U.S. cytogenetics capability and developing pre-positioned dosimeter concepts. Establish deployable hematology capability - radiation response team resource.	Establish a national cytogenetics laboratory network composed of reference laboratories supplemented with satellite scoring laboratories. Develop high-throughput sample-assessment system for radioisotope contamination. Pilot pre-positioned dosimeters.	Test system in well-controlled round robins and practice exercises. Establish standardized cytogenetics protocols and develop standard calibration curves.
Longer-range research on emerging dosimetry technologies	Initiate parallel efforts in emerging physical and biological dosimetry, define decision tree for technology assessment.	OSL, EPR and ultrasound: assess sensitivity, person-to-person variability, and safety of prototype systems. Hand-held breath gas analysis, blood cell counters, and triage medical recording/ tagging systems.	Develop working prototypes for con-ops and performance-based down select after ~year 5.
		Fortuitous dosimeters: develop con-ops, develop and assess field prototype detectors.	
		Molecular markers: demonstrate sensitivity, person-to-person variability / sensitivity to confounding factors; demonstrate field prototypes that meet sensitivity and other operational requirements.	
Demonstration programs	Define a field demonstration plan that leverages state and national exercises.	Conduct field demonstrations that verify performance of existing technologies.	Conduct field demonstrations of emerging dosimetry prototypes.

Supporting Information

A. Context for the Use of Emergency radiation Dose Assessment Tools

1. Event Characteristics and Diagnostic Requirements

Terrorist-driven exposure to radiation can result from several forms of R/N devices, ranging from non-explosive, clandestine exposure to a radiation source, to RDD, and even IND. Incidents may result in external exposure (radiation dose, without the presence of radioisotope(s) in or on the body) and/or the uptake of radioactive materials by inhalation, ingestion, skin absorption, wound contamination or injection of radioisotope(s) as embedded material. In many instances, emergency response personnel are the first medical responders to contact victims. In other cases, the medical treatment facility itself serves as the "first response" center. We did not include attack on a nuclear facility, as this scenario has already been well-studied and planned by the Nuclear Regulatory Commission.

A nuclear weapon detonation may result in exposure to (α) particles, (ß) emission, (γ)-rays, X-rays, and neutrons, with over 400 radionuclides possibly being released. However, only about forty of the released radioisotopes are likely to be hazardous to humans. (NCRP 65 1980; Durakovic, 1987; Cerveny, 1986). The most significant radioisotopes from unspent nuclear fuel are tritium, plutonium, and uranium. Radioisotopes of immediate medical significance include isotopes of americium, californium, cerium, cesium, curium, iodine, plutonium, polonium, strontium, and uranium, as well as tritium. (Cerveny, 1986)

For radioactive contamination, early information on the history of the exposure incident may identify the major isotopes involved and provide some dosimetry information. Causalities will likely present with no clinical symptoms other than possible conventional trauma. (Cerveny, 1989)

In most scenarios, the number and type of individuals that require evaluation changes, often significantly, over time following the event. In the first hour following detonation it is expected that there will be potentially 100's of treatable radiological causalities with external and internal radioisotope contamination and explosive trauma injury. At slightly later times (24 hours) victim makeup will likely shift to those with radiological contamination, minor trauma and many self-identified individuals who have some or no contamination but who still need evaluation. Beyond the first day, victims will likely consist of those who have some radiological contamination from plume exposure and many, potentially in the hundreds-of-thousands, who self identify with concerns about being exposed. for a nuclear weapon, many of those individuals are likely to be seriously exposed.

In response to the changing number and nature of the causalities, the types and needs of first responders and receivers also change. Initially, fire fighters, paramedics, law enforcement and good Samaritans will need tools for assessing radioisotope contamination and rapid dose assessment for triage in the field so that decontamination and life-saving activities can be managed. Later, high-throughput radioisotope contamination detectors and rapid dose assessment tools will be needed to assist with finding those in need of chelation, cytokine or other therapy and sending concerned citizens, with little or no exposure, home. Tagging victims in the early response phase following detonation will be crucial for longer term follow-up. Overall, there are four classes of device needs (here we focused on categories 1-3):

1. **Radioisotope contamination detectors and radionuclide dose assessment:**
   These detectors range from simple Geiger-Muller-type equipment to tools for assessing body fluids and other products, and potentially computational tools for converting measured counts or activity to an estimate of committed dose. Of equal importance is a simple, robust way to rapidly predict committed dose from detected counts. First responder con-ops will likely rely on such tools for early decision making on decontamination plans and whether it's necessary to intial more agressive threapies to limit possible or gun system failure. These concerns along with the first priority. First aid, will be important issues in the early stages of an event.

2. **Dose assessment tools that do not rely directly on counting radioactive emissions:**
   In many cases, particularly when significant dose is delivered from distant external radiation sources such as from ground shine, the level of radioactive contamination may not accurately provide an of estimate dose. The accuracy and threshold(s) for these tools depend on the type of triage / assessment need, particularly on whether other injuries are present.

3. **"You're ok" markers to avoid multiple evaluations of the same individual:**
   In all scenarios, the concerned citizens with no real exposure pose a significant and important component of those being assessed for potential radiation dose. Importantly, the number of these individuals is likely to measure in the thousands for all scenarios proposed.

Reliable discriminators to identify those who do not need further immediate care avoids the wasting of critical dose-assessment and response recovery resources.

4. **Tags for future tracking:**
Many individuals, often numbering in the thousands, both those who may need active care and those who do not, will be monitored for decades for long-term radiation effects. An efficient system for tagging these individuals and recording their initial location at the time of exposure will provide invaluable information for this long-term follow-up.

For each device, throughput and complexity are key considerations. The throughput requirements for each of the dosimetry devices depend on the type of scenario and time after the event when the device will be used. These factors affect the expected ratio of individuals to be assessed to number of responders and devices placed in use. Tolerance for device complexity depends on whether it is used by hospital personnel, firefighters, or even individual victims as a self-administered test and the environment in which the device is to be operated (i.e., in the field at the site of an event vs. in a hospital). However, in all cases, devices must feature simple sample collection, preparation, and results output, because of the likely confusion surrounding a radiological or nuclear event, compounded by their extreme rarity.

2. Triage and Initiation of Treatment

See recent International Atomic Energy Agency (IAEA) consensus guidelines for a comprehensive description of procedures for medical response during a nuclear or radiological emergency (IAEA, 2005). Requirements for sensitivity and dynamic range for emergency dosimetry strategies and technologies are related to current (and future) medical guidance for triage and initiation of treatment. Ideal medical management recommends early administration of treatment.

Lives may be saved if we can develop rapid dose assessment and can implement earlier treatment. Specifically, ideal medical management recommends early administration of treatment because much large animal data (Mc Vitte, 1996) and some human accident data (Gusev, Guskova, and Mettler) strongly suggests that early treatment with cytokines can significantly increase survival following large volume (>2 Gy) external radiation exposure to the hematopoetic system. This is because early cytokine therapy can prevent significant white blood cell depletion and the subsequent mortality from infections. There is a clearly identified gap in technology for identifying individuals with a clinically significant dose within the first 36 hours after exposure.

Radiation Injury Assessment and Triage Treatment.

Current civilian medical guidance (Waselenko, 2004) advocates two possible triage systems, one based on a modification of the military triage system (Walker and Cerveny, 1989) used in mass-casualty scenarios and another based on grading of clinical signs and symptoms (Dainiak, 2002; Fliedner, 2001). In the pre-dosimetry clinical signs and symptoms scheme, an initial response category is assigned by determining the degree of toxicity to the cutaneous, gastrointestinal, and neurovascular systems. Further categorization of patients based on hematologic degree of toxicity permits triage to an ambulatory setting, admission to a routine-care hospital floor, or admission to a critical care unit. This system is very useful to the clinician in management of a small-volume radiologic event. However, it is time-consuming and may be impractical in a large-volume scenario.

In the military-based triage system, priorities for treatment change, depending on how the patient is categorized in terms of radiation dose and the presence or absence of significant mechanical trauma or burns. (Waselenko, 2004)

> *"Individuals requiring surgical intervention should undergo surgery within 36 hours (no later than 48 hours) after exposure (Walker and Cerveny, 1989). Additional surgery should not be performed until 6 weeks later."*

Recommended triage priorities are summarized in Table 3, according to the Strategic National Stockpile – Radiation Working Group (Waselenko, 2004):

> *"At a whole body dose <1.5 Gy, triage categories remain the same: delayed treatment for those who are medically stable with significant injury but who may survive until definitive treatment is available; 2) immediate therapy for those with high survivability and significant injury, provided that immediate therapy is available; 3) minimal therapy for medically stable patients with minor injury; and 4) expectant therapy for patients who are seriously injured and in whom survivability is poor. All patients with the combined injury syndrome and exposure dose >4.5 Gy should be treated expectantly, except for those with minimal or no injury. Patients with radiation injury alone (i.e., without combined injury) should be triaged to the ambulatory setting if dose <1.5 Gy. For those with a higher exposure dose, routine care should include therapy with cytokines, antimicrobial agents, blood transfusion and frequent outpatient follow-up with laboratory monitoring."*

Consensus guidelines for treatment of radiologic victims (Waselenko, 2003) are summarized in Table 4. Radiation dose is

described as photon dose equivalent, and values are provided for adults (consider initiating therapy at lower radiation dose for non-adolescent children and elderly persons). Cytokines would be among the first agents administered to the group of significantly irradiated individuals who have the treated survival potential. A significant survival advantage has been demonstrated in irradiated animals treated with colony-stimulating factors (cytokines) in the first 24 hours. (Waselenko, 2004). Prophylactic Antibiotics are also a treatment component to be considered but should be addressed on a case-by-case basis.

Radioisotope Contamination

Thorough evaluation and estimates of internal contamination may take days or weeks, so initial decisions may have to be based only on local information and superficial measurements. Because rapid initiation of decontamination therapy both increases the effectiveness of the therapy and reduces the absorbed dose in the body, medical personnel must proceed quickly to obtain information and make treatment decisions based on available early estimates of possible exposure. Initial response will be to remove contaminated clothing and wash all contaminated victims to remove isotope from the body surface areas for those with external contamination. Therapy for internal contamination will likely begin somewhat later. Treatment risks must be weighed against the presumed risks of untreated exposure, and treatments for internal contamination should begin within hours of exposure. (NCRP Report 65, 1980; Durakovic, 1987, Cerveny, 1986; ICRP, 1955; Conklin, 1983; Moskalev, 1974; Cosgriff, 1987). More detailed radioisotope monitoring and radiation absorbed dose estimation may continue for days to weeks after treatment has been initiated. Although decontamination should be done as quickly as possible, the stability of an injured patient is vital, and first aid must be the primary concern (Cerveny, 1989) followed by removal of external sources of contamination.

3. Diagnostic Requirements for Sensitivity, Accuracy, Throughput and Turnaround Time

The military-based triage system, as well as the proposed consensus guidelines for treatment, assume a method for establishing radiation absorbed dose. Key decision points revolve around 1.5 and 4.5 Gy for triage, and 2-3 and 6-7 Gy for direct treatment of radiation injury. These action dose levels set a lower sensitivity limit of no greater than 1 Gy, and dosimetric uncertainties of less than about 20-30%. Because available data on exposure estimates have significant inherent uncertainties themselves, it is difficult to estimate the ideal dosimetric accuracy for emergency response and triage. Thus the above decision levels are based on the best available information and provide consensus starting points. Further research may be needed on this point.

Table 3. Priorities in triage of patients with and without combined injury, based on dose of radiation (military-based triage scheme). (Waselenko, 2004).

Conventional Triage Categories for Injuries without Exposure to Radiation*	Changes in Expected Triage Categories after Whole-Body Radiation		
	<1.5 Gy	1.5 – 4.5 Gy	>4.5 Gy, ≤ 10 Gy
Delayed	Delayed	Variable	Expectant
Immediate	Immediate	Immediate	Expectant
Minimal	Minimal	Minimal	Minimal
Expectant	Expectant	Expectant*	Expectant*
Absent	Ambulatory Monitoring	Ambulatory monitoring with routine care and hospitalization as needed	

*Although other injuries may be minimal, treatment guidelines should be followed for patients receiving a whole-body radiation dose greater than 3 Gy.

Table 4. Guidelines for treatment* of radiologic victims. (Waselenko, 2004)

Variable	Proposed radiation dose range for treatment with cytokines	Proposed radiation dose range for treatment with antibiotics	Proposed radiation dose range for referral for stem-cell transplant consideration (SCT)
Small-volume scenario (≤100 casualties)			
Healthy person, no other injuries	3-10 Gy	2-10 Gy	7-10 for allogeneic SCT; 4-10 if previous autograft stored or syngeneic donor available
Multiple injuries or burns	2-6 Gy	2-6 Gy	
Mass casualty scenario (>100 casualties)			
Healthy person, no other injuries	3-7 Gy	2-7 Gy	7-10 for allogeneic SCT; 4-10 if previous autograft stored or syngeneic donor available
Multiple injuries or burns	2-6 Gy*	2-6 Gy*	NA

* If resources are available. ; see reference (Waselenko, 2004) for additional details.

Ideal timescales for obtaining dosimetry information can be estimated from optimal therapy initiation times. Radionuclide decontamination treatment should be initiated within hours of exposure. For direct treatment of radiation injury, cytokine therapy should be initiated within less than 24 hours after exposure, leading to a goal of completing initial triage / screening for radiation injury victims within this 24 hour time frame. Upper limits for processing time may be related to onset of radiation sickness syndromes, which would presumably make radiation exposure self-evident. However, in the case of a nuclear weapon detonation, presence of high radiation levels may prevent access to the scene for 24 hours or more. Thus turn around time of less than 24 hours is needed for maximal benefit from such therapy. The gastrointestinal syndrome follows a latent period of 5-7 days. Cytopenia associated with the hematopoietic syndrome becomes evident within 24-48 hour for lymphocytes, 5-30 days for neutrophils, and ~15 – 30 (nadir) days after exposure. If identifying patients substantially before gastrointestinal syndrome onset is used as an upper limit for processing times, 3 days seems to be a reasonable upper limit for processing patients who have been potentially lethally exposed to radiation. Beyond 5-10 days, the gastrointestinal syndrome is self-evident and blood counts may serve as a reasonable indicator of exposure for predicting hematopoietic syndrome.

These timescales suggest an ideal assay processing turnaround time of 24 hours. For throughput estimate purposes, assume a processing goal of initial assessment completed within 24-72 hours, and an estimated 100,000 individuals to be evaluated (this could be a representative figure for expected radiation injuries for fallout following a nuclear weapon explosion, and would include mostly concerned individuals for most radiological dispersal scenarios). Also assume 100 individuals to be assessed in parallel. To achieve the evaluation within these parameters, the initial triage bioassay for each individual radiation-injury assay must be completed in 1-4 min. Clearly, this is difficult to envision without additional investment in technology enhancements.

B. Current Methods and Tools for Triage and Emergency Dose Assessment

The consensus generic approach for medical management of radiation casualties involves use of multiple parameter biological symptoms and bioassays, physical dosimetry, and radioactivity contamination for radiation injury and dose assessment. Individual dose assessment is essential for predicting the clinical severity, treatment, and survivability of exposed individuals and identifying those with minimal or no exposure.

In the case of a radiological mass casualty incident the initial triage response should focus on screening these large populations for clinically significant doses with 1-Gy threshold sensitivity. The individual technology components, including physical dosimeters, of the multiple parameter dose assessment approach, need Food and Drug Administration regulatory review and approvals if applied for medical treatment decisions.

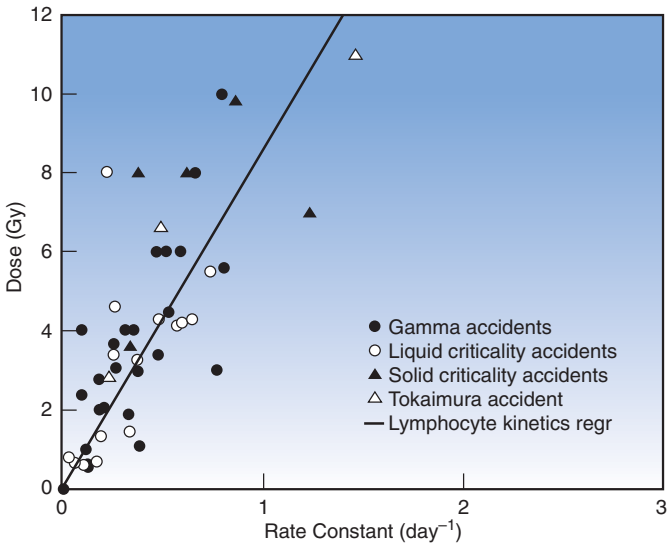
This section describes current methods and instrumentation that could be used for triage and emergency dose assessment.

1. Biological and Clinical Signatures of Radiation Dose Assessment

Currently, the three most useful biological / clinical signatures determining radiation injury and dose assessment are time to onset of vomiting, lymphocyte depletion kinetics, and the presence of chromosome aberrations (Waselenko, 2004). A radiation casualty management software program, the Biological Assessment Tool, is available at the Armed Forces Radiobiology Research Institute's Web site (www.afrri.usuhs.mil). This tool was developed in collaboration with the Radiation Emergency Assistance Center/Training Site (REAC/TS) and others to facilitate medical recording and estimation of individual dose (Sine, 2001). The International Atomic Energy Agency (IAEA) has developed generic guidelines for recording clinical signs and symptoms of radiation injury (see www.iaea.org). Using a grading system for the severity of clinical symptoms, the Medical Treatment Protocols team has developed a quantitative system to assess individual biological response to radiation exposure when results of chromosomal analysis are not yet available (Fliedner, 2001).

The time-to-onset and percentage of victims with vomiting is related to radiation dose received. Greater than 90% of those receiving 6 Gy or more will present with an average time-to-onset of vomiting within an hour. In the 1-3 Gy range, about 50% of victims show signs of vomiting, with an average time-to-onset of greater than 2 hours. However, this assay relies on victim recall and results are variable among individuals.

Absolute lymphocyte counts decrease with increasing dose and increasing time from exposure. In the first 12 hours, only doses of 9 Gy and higher are expected to result in absolute lymphocyte counts that exceed the lower normal bound. This lower bound will be exceeded for approximately 5 Gy and 3 Gy exposures, after 24 and 48 hours, respectively. The rate constant for lymphocyte depletion increases with dose. Figure 1 shows the considerable variation in lymphocyte kinetics and time-to-vomiting, based on accident victim data. (Goans and Waselenko, 2004).



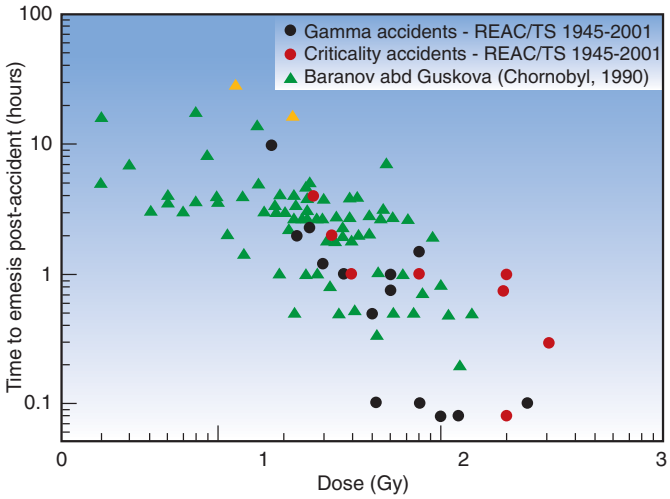


Figure 1. Dose response calibration curves for lymphocyte depletion kinetics and time-to-vomiting. These data illustrate the radioresponse for two major indicators used to provide a triage dose assessment based on radiation doses of record derived from gamma ray accidents, criticality accidents, and Chernobyl (Goans and Waselenko, 2004: presented at the 2004 NCRP annual scientific meeting).

Dose assessment based on cytogenetic – chromosome aberration biodosimetry represents a well established and proven bioassay for radiation dose assessment (10-cGy threshold in a good laboratory). Radiation exposure induces many types of chromosomal aberrations in the exposed individual's peripheral blood lymphocytes. The presence of dicentrics, a chromosomal aberration, in an individual's peripheral blood lymphocytes indicates radiation exposure (Bender and Gooch, 1966). Dicentrics are considered relatively radiation specific; only a few chemicals are known to interfere with the assay. Low background levels (about 1 dicentric in 2000 cells), high sensitivity (a threshold dose of 0.05 Gy), and known dose dependency of up to 5 Gy (for acute photon exposures) make this assay robust and a "gold standard" biodosimetry method.

The IAEA published a technical manual containing a harmonized methodology for various cytogenetic assays (IAEA, 2001). An International Organization for Standardization (ISO) working group was established to standardize biological dosimetry by cytogenetics. Under the auspices of the ISO, regulatory compliance and validation standards have already been developed (Voisin 2002). This ISO working group is now focusing on developing the standard titled "Radiation Protection — Performance Criteria for Service Laboratories Performing Cytogenetic Triage for Assessment of Mass Casualties in Radiological and Nuclear Emergencies." This standard will define the process and identify quality control standards for the use of cytogenetic methods to rapidly assess radiation dose, information that will supplement the early clinical categorization of casualties.

The use of cytogenetic assays to guide treatment decisions was demonstrated in radiation mass casualties for example, Chernobyl, Goiania, and Tokaimura. Dose estimates from

cytogenetic methods correlate well with the severity of acute radiation syndrome (Sevan'kaev 2000). In the Chernobyl accident an approximate dose estimate was achieved by rapid preliminary examination of metaphase spreads (Pyatkin 1989). From the Goiania (Brazil) accident cohort, 129 exposed or potentially exposed individuals were investigated by cytogenetics (Ramalho and Nascimento 1991). More recently, in the Tokaimura, Japan, criticality accident, the dicentric and premature chromosome condensation (PCC) assays were used to assess the dose for three severely exposed workers (Hayata 2001; Kanda 2002) and 43 resident workers (Sasaki 2001).

Rapid response is required from specialized cytogenetic biodosimetry laboratories in the case of a mass-casualty scenario for potentially thousands of individuals (Voisin, 2001; Prasanna, 2003). Due to requirements inherent in the standard assay, results are not available for 48 to 72 hours after the sample has been submitted for analysis. These time gaps make standard cytogenetic bioassay an important tool for biodosimetry, but not for direct use at the emergency scene. A requirement for the emergency scene, however, is obtaining blood samples with a well-defined protocol, possibly using a kit-type approach diagnostic laboratory.

While standard cytogenetic assays require days to complete, speed and throughput of the dicentric assay could be adapted for mass casualty triage (Lloyd 2000; Voisin 2001; Prasanna 2003). Faced with an urgent need for rapid results, clinical triage can be accomplished by scoring as few as 20 metaphase spreads per subject, compared with the typical 500 to 1000 spreads scored in routine analyses for estimating dose. For example, Lloyd (1997), after studying lymphocyte chromosome damage in 10 of the 13 severely irradiated Chernobyl victims, suggested that the frequency of metaphase spreads without dicentric aberrations can be used to identify patients suitable for cytokine therapy versus bone-marrow transplantation. In addition, sample processing throughput of cytogenetic laboratories can be increased by using robotic instruments, metaphase harvesters and spreaders, etc. Commercially available laboratory information management systems (LIMS) can be customized for dealing with the data and sample management challenges inherent in requests to process large quantities of samples for dose assessment. However research is needed to determine whether cytogenetics will have the necessary sensitivity (1 Gy) to detect clinically significant doses when applied in an emergency situation to large populations. At present, to deal with such a situation multiple laboratories with common methods and calibrations will likely be needed to meet throughput, speed and sensitivity requirements.

Other approaches have been explored as well including the use of somatic null mutations at the glycophorin A locus on the surface of blood erythrocytes, micronucleus assay, and measurement of premature chromosome condensation, PCC and all have been found to be reliable indicators of exposure over a broad dose range (0.25 to 8 Gy) in the laboratory with high doses of ionizing radiation but with poor dosimetric discrimination at lower doses (Bigbee et al., 1997; Gray and Pinkel., 1994; Jones et al., 2001; Brown et al., 1997; Tawn et al., 2003; Bedford and Dewey, 2002; Durante 1996; Kanda 1999). Variations of the PCC assay (Prasanna, 2000) may provide dose estimates in less than 24 hours for relatively high doses of ionizing radiation, but still require validation.

In the last decades, the use of fluorescence *in-situ* hybridization (FISH) to label specific chromosomes has allowed the easy detection of chromosome translocations, which can persist for decades after exposure (Lucas, 1992). Translocations have played a fundamental role in determining the radiation dose received by individuals exposed during the Chernobyl nuclear accident (Moore et al., 1997; Jones et al., 2001). Translocations can provide a very precise assessment of radiation dose; however, the experimental method requires skilled personnel and expensive equipment. Additionally, the assay requires several days to a week to be completed and therefore cannot be used to obtain a fast estimate of the dose during the first few days after exposure when the information would be most critical for identifying victims of radiation accidents who could benefit the most by medical intervention.

Given cytogenetics current standing as the best accepted assay for radiation dose assessment and its limited throughput, we advocate that a national network of laboratories linked by standard methods and calibrations should be re-established to handle the potential surge in analysis needed in the event of an R/N event and this network should be integrated into the a national radiation protection program. Development of national biodosimetry network of reference laboratories could provide capacity needed to respond to a large scale or multi-site R/N incident.

In summation, research is needed to address the potential for more rapid cytogenetics, to develop standardized Food and Drug Administration approved assays and to develop a network of laboratories that can respond to a mass causality event. However, methods for its improvement should be encouraged

and inter-laboratory variability in this bioassay needs to be characterized.

2. Dosimetry and Location-Based Dose Assessment

Physical dosimetry using pre-positioned dosimeters currently serves as a mainstay in the military, as well as all organizations in which personnel could be exposed to ionizing radiation. Personal dosimeters of this type exist in the form of film, thermoluminescent dosimeters, or track-etch devices.

Since radiation fields are typically determined during the early response of a radiological exposure, an individual's time and locations at the radiation incident scene should be recorded so that they can be used for dose reconstruction applications.

In the special case of neutron exposures, derived from a criticality incident or IND, an assessment of internal radioactivity contamination due to neutron activation in blood, urine, and hair is an approach for estimating prompt neutron dose. The presence of high background radiation, however, may make this approach an infeasible early response diagnostic technology for a nuclear event.

Dose estimates can be made through knowledge of the time an individual spent at a particular location if there is information on the radiation contamination in the environment for that area. Hence, information should be collected on the victim's whereabouts relative to the source of radiation such that their accumulated external dose can be quickly estimated using simple hand-held calculating devices or from more complex models which would take much longer to determine.

The external dose received by an individual who has spent time in an area that has received contamination from a radiological dispersal device is proportional to the initial exposure rate they were subjected to and the time spent in that area. Hence, the critical information needed to assist triage decisions are: (1) the location of the exposed person, either relative to the site of the explosion, or relative to the site of the nearest measurement of exposure rate (or dose rate to air), and (2) the length of time spent in the area where radiation was received. Such an assessment assumes, of course, that the person did not receive prompt radiation from a fission event, but was only exposed to either residual radiation, fallout, or dispersed radioactive materials.

For example, the dose to a specific tissue, or the whole body, can be estimated as shown below, assuming that the exposure rate is nearly constant during the time spent in the contaminated area.

$$D_T = t\,(W/e)(D_T/K_a)$$

where,

D_T = tissue absorbed dose (Gy)

X = exposure rate (C kg^{-1} s^{-1}, where 1 R s^{-1} = 2.58 x 10^{-4} C kg^{-1} s^{-1})

t = time (s) spent at location with exposure rate as described

W/e = mean energy expended in air to form an ion pair ≅34 J/C

K_a = air kerma (Gy)

Note that values of D_T/K_a can be obtained from numerous sources, e.g., ICRP 74 (1996).

If the exposure rate is changing substantially during the exposure period, then the dose to the person can be estimated from an integration of the dose rate over the exposure time:

$$D_T = \left[\int_{t_o}^{t_e} \dot{X}(t)\,dt\right](W/e)(D_T/K_a)$$

where t_o is the time that exposure began, and te is the time that exposure ended. In the case of radioactive fallout, the radiation field decays approximately by the power law of $t^{-1.2}$:

$$X = \int_{t=TOA}^{t=t_e} \dot{X}_{TOA}\left(\frac{t}{TOA}\right)^{-1.2} dt = 5\ \dot{X}_{TOA}\,TOA^{1.2}\,(TOA^{-0.2} - t_e^{-0.2})$$

where,

X is the integral exposure expressed in milliRoentgens (mR) from TOA until t_e,

TOA is the time elapsed from the detonation until the arrival of the debris cloud (h),

X_{TOA} is the exposure rate at TOA (mR/h).

Since the time of measurement would undoubtedly be later than the time that exposure began, a simple decay correction can be from time of measurement, t_m, to the time when exposure began, t_o (again, assuming fallout from a nuclear detonation):

$$\dot{X}_{TOA} \cong \dot{X}_m \left(\frac{t_m}{t_o}\right)^{1.2}$$

[1]Here *exposure* rate is used in the technical sense of the rate of ionization in air, i.e., 1 Roentgen s^{-1} = 2.58 x 10-4 C kg^{-1} s^{-1}. Note that the dose to a person could also be determined from the dose to air.

If the exposure is due to a single radionuclide, then the equations can be modified for its half-life and energy.

Calculations such as those described here could be facilitated by use of pre-programmed hand-held instruments (HHAs; calculators, Palm Pilots, etc.). In that case, the person who is responsible for the crude estimate of external dose (as described above) would need to input the following data: exposure rate (R/s) measured at a location relatively close to victim, the time of measurement, approximate time when exposure began, approximate time when exposure ended (i.e., when victim was removed).

If exposure rate measurements at the precise location of exposed victims are not available, measurements made nearby to the victim could be substituted with the restriction that both the measurement and the victim were subject to approximately the same shielding.

In the case of a radiological terrorism event, it would seem that quick calculations via handheld devices would be possible, but would require that the outcome of that assessment be physically or virtually attached to the identity of the person, e.g., via a database including a photograph. During the chaotic situation that would follow such events, maintaining the dose assessment information with the victim will prove difficult.

3. Measurement of Radioisotope Contamination

The Centers for Disease Control is currently leading an effort to provide high-throughput bioassay of internal radioisotope contamination. While critical for medium- and long-term assessment, internalized radioisotope contamination dosimetry does not contribute to decisions made within the first 72 hours after initial exposure. Decorporation decisions will be driven primarily by the threat and relevant decontamination agent(s) available to be brought to bear. In addition, contamination from nose swabs and clothing should be captured as part of an overall initial assessment, and estimation of internal contamination is important for long-term patient management.

If patients are few and there is an evident need to determine the total internal radiation dose, all body effluents should be collected for an extended time. Measurements of excreted radionuclides will provide information required to estimate the total internal body burden. (NCRP 1980) Depending on the internally deposited radionuclide and its physicochemical characteristics, the collections may have to be made for months. For example, radionuclides with long radiological and biological half-times would need to be monitored longer than radionuclides with a short radiological or biological half-time. Radionuclides inhaled in relatively insoluble form would need to be monitored longer than more soluble forms due to the potentially extended residence in the lungs.

4. Pre-positioned Physical Dosimeters

Physical dosimetry using pre-positioned dosimeters currently serves as a mainstay in the military, as well as all organizations in which personnel could be exposed to ionizing radiation. Personal dosimeters of this type exist in the form of film, thermoluminescent dosimeters, or track-etch devices.

Measurement of neutron activation of sodium in blood or sulfur in hair is an approach that has been demonstrated in the laboratory for estimating prompt neutron dose. However the presence of high background radiation may make such measurements infeasible for use as a neutron dosimeter following an R/N event.

A new device, the Self-indicating Instant Radiation Alert Dosimeter or SIRAD™ (see www.jplabs.com for more information) is a low-cost, disposable dosimeter that is packaged similar to a credit card. This devise presents the possibility of producing a low-cost, preposition civilian monitoring dosimeter. The sociological dimensions of wide distribution of such a device provide one of the greatest uncertainties for its deployment for use by the civilian population. Nevertheless, this type of technology, while relatively new, is a very exciting development for the field of personal dosimetry and should be evaluated for its value in a radiological or nuclear event.

C. Assessment of Emerging Dosimetry Technologies

1. Biological Measurements

A variety of biological materials can and have been used for diagnostic purposes in clinical medicine and forensics. These include blood, saliva, interstitial fluids, breath, exfoliated cells, tissue samples, hair, urine and feces. These range in the risks and complexity of collection from hair and saliva for rapid safe and simple collection to sampling of internal tissues by biopsy which is complex and presents health risks to the casualty. We considered technologies that could be applied to any biological sample but expect that diagnostics will be limited in practice to samples that can be easily collected in a rapid fashion with little risk to the potential causality or responder. We also limited our evaluation to samples which responders are accustomed to dealing with and for which a supporting research literature base exists. We judged the most promising sample sources to be exfoliated cells, body fluids such as blood and saliva, and breath. Use of hair, tissues and other body fluids require risky, time consuming, complex collection procedures, are not generally handled by first responders, or have a limited supporting research base.

Molecular Markers in body fluids and tissues

Biomarkers are specific chemical or biological properties that can indicate a health-related process or outcome. They constitute molecules as diverse as proteins and small molecule metabolites. Biomarkers have been under intensive research for many decades and many reviews and books have been written on them and their use (Blakely et al., 2001; Mendelsohn, Mohr, and Peeters, 1998; Gledhill and Mauro, 1991 as examples). Biomarkers represent underlying changes in physiology which can arise from physical damage (cell lysis and the release of intracellular proteins into the circulation, oxidation by-products or DNA breakage), underlying changes in biochemistry (presence of new metabolites or changes in levels of key gene products), and / or changes in cellular composition of tissues. Biomarkers have been proposed for and used to diagnose the presence of infectious agents, to judge the damage caused by exposure to chemicals, to judge one's individual susceptibility to disease, to predict medical outcome and therapy, to measure organ system function, and to predict prognosis or health outcome for damaging exposures or disease. Likewise, it has been suggested by several expert panels that such markers could be useful in responding to an R/N incident particularly to enable rapid triage of at-risk populations (young, aged, those with significant health conditions) from potentially exposed individuals and to guide treatment and post-radiation victim care (NIH, 2005, JIWG, 2005; Trent Congressional Testimony at http://kyl.senate.gov/legis_center/subdocs/051104_trent.pdf).

The steadily increasing sophistication in our understanding of the early biochemical responses of irradiated cells and tissues provides the opportunity for developing mechanism-based biosignatures of exposure (Woloschak & Paunesku, 1997; Fornace et al., 1999; Tusher et al., 2001). Compelling breakthroughs have been made in the technologies for genome-scale analysis of cellular transcriptional and proteomic profiles (Chee et al., 1996; Lockhart et al., 1996; Lipshutz et al., 1999; Jain, 2002; Kukar et al., 2002; Issaq et al., 2003; Krieg et al., 2004), in the quantitation of biomolecular signatures, and in advanced statistical and bioinformatics methods to analyze large biological data sets (Dudoit et al., 2000; Werner, 2001; Peterson, 2002; Peterson, 2003). There have also been major strides in the mechanistic understanding of the early events in DNA damage and radiation damage products, as well as in the cellular pathways that lead to radiation injury (Thompson & Schild, 2001; Burma & Chen, 2004; Fernet & Hall, 2004; Kurz & Lees-Miller, 2004; Meek, 2004).

New research with genomic- and proteomic-wide tools is showing that within minutes to hours after exposure to ionizing radiation proteins are modified and activated, and large-scale changes occur in the gene expression profiles involving a broad variety of cell-process pathways (Amundson et al., 1999; Park et al., 2002; Kang et al., 2003; Yin et al., 2003). High-throughput gene expression profiling in human peripheral blood lymphocytes irradiated *ex vivo* and other human cells have identified several genes, such as GADD45 and CDKN1A, whose expression increases as function of the ionizing Radiation (IR) dose (Amundson, 1999; Blakely et al., 2001; Kang et al., 2003). Transcriptional changes should correlate with changes in protein expression, and a recent survey of the literature has identified several proteins that provide evidence of exposure over a range of dose and time.

A review of the literature suggests that there are presently approximately 90 known proteins that show changes in expression or undergo post-translational modifications after exposure to ionizing radiation. Some of these change in a dose dependent fashion although there is limited data on the shapes of dose- and time-response curves. To date, most of these proteins (approx. 90%) were identified using *in vitro* tumor cell models and the majority of research has been with high doses of ionizing radiation (> 4Gy). Few human- or animal-based studies have been reported and limited validation of the use of molecular biomarkers for radiation injury assessment has taken place in clinical populations although some validation of the value of

molecular markers for judging biological dose for ionizing radiation is now being published and appears promising (Lesli, 1992; Beccossi, 2001). Serum amylase, for example, is a case where clinical assays presently exist and where there is data suggesting radiation responsiveness.

Although more research is needed, the wealth of information generated by these studies provides the foundation for developing mechanism-based biosignatures of exposure that correlate with the timing and dose of radiation exposures. In addition, the rapid explosion of proteomic/genomic/metabolomic technologies and innovations and their application to the systematic characterization of the proteomic, genomic and metabolomics profiling of healthy human tissues and serum (Tirumalai et al., 2003), provide baseline references for identifying early biomarkers of radiation exposure and of tissue-specific damage. At present, even though there are significant limitations in extrapolating the value of the nucleic acid, metabolite or proteins discussed above to the human R/N threat scenarios, a set of proteins or mRNA targets do seem to offer potential for use as biomarkers (see Table 5).

Table 5. High-priority candidate radiation-responsive proteins for biomarker development

	Protein	
Priority Group	**Symbol**	**Name**
1	**ATM**	ataxia telangiectasia mutated
	H2AX	Histone 2AX
2	**CDKN1A**	cyclin-dependent kinase inhibitor 1A (p21, Cip1)
	DDB2	amage-specific DNA binding protein 2
	GADD45A	growth arrest and DNA-damage-inducible 45 alpha
	PCNA	Proliferating cell nuclear antigen
	CCNB1	cyclin B1
3	BLM	Bloom syndrome protein
	RPA1	replication protein A1
	Tp53	tumor protein p53
	CHK2	checkpoint kinase
	CDK4	Cyclin-dependent kinase 4
	CDKN2A	cyclin-dependent kinase inhibitor 2A (p16)
	ENO1	enolase 1
	ERP 29	similar to Protein disulfide isomerase A4 precursor

Proteins with data from more than one species are indicated in bold.

However, while recognition of the gap in available early and rapid technologies for radiation dose assessment has accelerated research into the applicability of molecular markers as indicators of radiation dose, at the present time, this technology is in its infancy. Research into the discovery of markers indicative of radiation exposure is primarily being carried out in academic institutions and government laboratories. No commercial assays have been developed or marketed and there presently is little effort in the industrial sector to develop such assays for radiation dosimetry or triage. Likewise little R&D funding has been directed towards development of commercial assay concepts and prototypes (although some funding is being provided by Department of Defense and the National Institutes of Health will fund some centers and increase spending in the near term to conduct such research). Research is needed to understand how these markers respond to different types of radiation (radiation quality factors), how these markers relate to known clinical or biologically relevant effects and dose rate effects. There is a critical need to understand the normal expression range of potential radiation markers in healthy people as well as groups with pre-existing health conditions. Additionally, an understanding of the time and dose kinetics and effects of other confounding factors such as age, gender, and genetic background needs to be understood. The value of single parameter versus multi-parameter signatures should also be evaluated. Analytic models based on quantitative data using various model systems are required. An understanding of sensitivity and specificity of potential molecular markers is needed. Statistical methods to evaluate and interpret assay results needs development and validation. Research is also needed into judging the value of these biomarkers for indications of latent radiation responses even though initial efforts may focus on the diagnostic information for acute early-response. While most research and technology development has so far centered on genomics and proteomics, other potential molecular classes could prove useful as indicators of radiation dose also and should be investigated. In particular research is beginning on small molecule metabolites, lipids, and glycosylated, biomolecules. National efforts in this regard can be significantly aided by international research efforts and experiences.

Breath Gas Analysis

Another promising area for biological measurement of radiation injury is breath analysis. The vast majority of tissue damage following irradiation results from the action of free radicals produced by the absorption of ionizing radiation. Free radical-induced damage is associated with the process of lipid peroxidation

of omega-3 and omega-6 fatty acids (Sies 1997). End products of lipid peroxidation of polyunsaturated fatty acids are ethane and pentane and the intermediate malandialdehyde. No other major endogenous sources of ethane and pentane are anticipated other than lipid peroxidation (Kharitonov and Barnes 1994).

Breath ethane generation was measured by Arterberry et al (1994) during clinical total body irradiation for treatment over a 4-day period. The largest changes in breath ethane occurred on day 2 and these changes were correlated with clinical manifestations of gastrointestinal side effects. Since the study by Arterberry et al (1994) several authors have explored more sensitive methods for measuring breath gasses. The study by Mueller et al (1998) evaluated breath analysis of exhaled air by mechanically ventilated patients using microwave energy desorption coupled with gas chromatography-flame ionization detection-mass spectrometry. Infrared laser spectroscopy was used by Basum et al (2003) who were able to detect in near real-time 500 ppt ethane. Malandialdehyde is a well developed diagnostic for lipid oxidation but little is known of its utility as a marker of radiation exposure. Other molecules are also present in breath and efforts have been made to explore their utility for disease diagnostics.

These studies suggest the possibility of breath analysis as a tool to support triage following an IND/RDD event. However, these gases are associated with a variety of medical conditions that may complicate future attempts to use breath analysis to estimate absorbed radiation dose. Research is needed on how well they relate to radiation dose.

Devices for Biological Indicators of Radiation Injury

A vast array of technologies is being developed and applied to researching biological indicators of disease and is being developed for use in diagnosis. Platforms have been developed for analysis of proteins, DNA/RNA, molecules in breath, small molecule metabolites, cells and others. These are generally based on DNA microarray, Polimerase Chain Reaction (PCR) based assays (PCR), protein array, multiplexed-antibody assays, lateral flow immunoassay (LFD), mass spectrometry, various chromatography's, spectroscopic analysis, image analysis, flow cytometry and SAGE (serial analysis of gene expression). A variety of companies have proprietary platforms for conducting these analysis including, as examples, Luminex for multiplexed antibody assays; Affymetrix for DNA microarrays; Litron Laboratories for flow cytometry-based methods for cytogenetic damage; Loats Associates for automated micronucleus assay; and Metabolon for metabolic pathway mapping. While many technologies have been developed, none are available for molecular diagnostics of radiation injury (see Baker, 2005) and few are available for cell analysis.

The simplest promising device that has applications for radiation biodosimetry triage is the lateral flow immunoassay device (LFD). LFDs are a common diagnostic assays employed in clinical laboratories. Most people are aware of the use of this format in over-the-counter pregnancy tests. Laboratory tests are available to the clinician for fertility, pregnancy, infectious disease, veterinary, and food safety applications, and new ones are being developed at a steady rate (eg, Quach et al., 2002, O'Keefe et al., 2003, Slinger et al. 2004, Cazacu et al., 2004). In addition, the US military uses this format in the field to detect biological warfare agents with their Hand Held Assays (HHAs). These can be run by hand or employed in automated systems. In 2004, the US military produced over 9 million HHAs. The anthrax letter that was sent to Senator Daschle was tested on site with an HHA which shut down the congressional mail and prevented the letter addressed to Senator Leahy from being opened.

As mentioned, while a variety of technologies, tools and methodologies have been developed to discover, characterize and analyze proteomic, metabolomic, and genomic, markers for diseases, there is no commercial assays available for radiation biodosimetry and limited evidence of development in this area. There are few patents for radiation biodosimetry diagnostics, few awarded research proposals, and some requests for proposals in this area from the Department of Defense and the National Institutes of Health. However, since significant industrial effort is being devoted to development and marketing of diagnostics for other health-related conditions (cancer, infectious disease, etc) it should be possible to rapidly develop and commercialize radiation dosimetry tools once the basic research finds and validates relevant molecular indicators of radiation exposure. Research investment is needed in exploring the development of such tools specifically for radiation biodosimetry, their con-ops and optimal systems architectures in the environments for which they will be used.

2. Physico-Chemical Measurements

We have identified several concepts that make use of changes in physico-chemical response that may afford adequate dosimetry characteristics for human tissues and artifacts that humans may carry on their person. Prior investment in attempting to

capitalize on these characteristics is uneven and therefore it is difficult to provide inter-comparisons with respect to potential. For example, optical stimulation of luminescence (OSL) is a well-defined science supporting commercial dosimetry systems for workers in nuclear facilities. But the use of teeth or bone as dosimeters represents additional technological challenges. Electron parametric resonance (EPR and also called ESR), on the other hand, has been used essentially exclusively for retrospective epidemiology studies and currently requires an extracted tooth, an invasive procedure not likely in the first hours after a large terrorist event. We present concepts below that vary considerably in underlying technologies. While there certainly are additional concepts, we will focus on the following:

- Luminescence
  - —Teeth and Bone
  - —Fortuitous Dosimeters
- Electron Parametric Resonance
- Breath Analysis
- Ultrasound

Luminescence

Estimating dose from physical measurements has been under investigation for some time. Dose response luminescence of a wide variety of natural and manufactured materials has been studied since the early decades of the 20th century. Initial experiments concentrated on prompt phosphors and photoluminescence, however technical improvements in fine control of thermal profiles led to the development of thermoluminescence (TL) as a reliable means of detection of radiation doses absorbed by a variety of natural and manufactured wide-gap insulators. Understanding of the dose response TL behavior of natural materials, primarily quartz and feldspar, was given a tremendous boost by a key group at Oxford University in the 1960's to 1980's (Aitken, 1985). Although their focus was the chronology and authentication of archaeological objects, the basic research carried out by members of the group led to methodologies suitable for the detection of very low absorbed radiation doses and therefore to retrospective dosimetry.

The recognition that exposure to sunlight of natural geological deposits results in a depletion of their TL signal led to the invention of optical dating (Huntley et al., 1985). In this technique, dose response luminescence is stimulated optically rather than thermally, as in TL. OSL, in which stimulation is provided by infrared or visible photons rather than heat was quickly recognized as providing a number of advantages over TL. For example, with a short pulse of stimulating light, the trapped charge population may be sampled rather than completely erased as it is in a TL measurement; different wavelengths of light, tailored for optimal luminescence response in different minerals may be selected; a wide or narrow detection region is achievable with appropriate stimulating photons or with pulsed rather than continuous stimulation; and a high concentration of stimulating photons permits the detection of luminescence from an aliquot as small as a single sand-sized grain of quartz with a mass of ~2 µg rather than a typical aliquot of ~5 mg. In addition, transmittance of both stimulating photons and emitted luminescence via fiber-optic cables is easily achievable, thus permitting a degree of flexibility and optimization of instrumentation design simply not possible with TL. OSL may also be detected simultaneously with TL or, if the sample is being continuously irradiated, with radioluminescence (RL). Many of these potential advantages have been discussed and implemented within the past two decades (Aitken, 1998; Bøtter -Jensen et al., 2003).

Optical Stimulation of Teeth and Bone

A portable OSL dosimetry instrument that could be used on an intact person has been suggested by Godfrey-Smith and Pass (1997). The key advantage of such an instrument is that it would use photons rather than electron resonance to stimulate luminescence (Huntley et al., 1985), and therefore any risks associated with its use should be no more dangerous (in principle) than shining a strong light into a person's mouth.

The key observation of the initial investigation of the OSL properties of tooth enamel is that both infrared and visible green photons are capable of stimulating luminescence, and that the dose response is detectable in both a broadband visible region (when stimulated with IR photons) and in the near-ultraviolet (when stimulated with green photons). Godfrey-Smith and Pass (1997) also showed that signal response is stronger in non-deproteinated tooth enamel versus deproteinated enamel. The net initial count rate for non-deproteinated enamel was 2.6 cps·Gy^{-1} for IR stimulation and broadband detection. For a background rate of 20 cps, a dose of 15 Gy should be readily detectable in non-deproteinated enamel: i.e., whole teeth, with an S/N ratio of 3, with no

changes in instrumentation from the initial equipment. One may deduce from this that steps toward the optimization of stimulating wavelength, its incident intensity, spectral width of the detection band, and the tooth-to-detector geometry should make the detection of much lower (10X) doses readily achievable. Such optimization could bring the lower limit of detetion to approximately 0.25-0.5 Gy.

Optical Stimulation of Fortuitous Dosimeters

Members of the public do not carry calibrated radiation dosimeters like those provided to radiation workers, but there are a number of common materials often in their possession or nearby that can serve as dosimeters for evaluating the degree of radiation exposure from an incident. Radiation dose from X-rays, gamma (γ) photons and beta (ß) particles can be measured using diamonds and other semi-precious stones in jewelry; semiconductor components in cell phones, personal digital assistants and car keys, quartz in watches and watch faces, and even tooth enamel. All are materials that store energy from ionizing radiation as unpaired electrons trapped in elevated energy states. These unpaired electrons can be detected and measured a number of ways: – by EPR, TL, and OSL – to determine the radiation dose. Alpha (α) particles from the dispersion of uranium and transuranic radioisotopes and neutrons from nuclear devices can be measured by treatment of glass and many plastics, including those used in watch covers and eyeglass lenses. Other radiation-sensitive materials in buildings and soil can be used to determine isodose curves around the radiation event. Quartz, used widely for radiation damage dating of archaeological artifacts, is ubiquitous in soil and building materials, and its man-made counterpart is the principal component of fiber-optic cable. Even common table salt can serve as a radiation dosimeter.

Determining the radiation dose from a fortuitous (un-calibrated) dosimeter material subsequent to its exposure requires two steps. The first step involves measuring the "as-found" signal from the material. The second step requires exposing the sample to a known radiation field and measuring the additional response. The sample's radiation sensitivity, from the second step, is then used to evaluate the "as-found" dose from the first step. This practice was used in the reconstruction of doses to A-bomb survivors with, for example, tile and brick, heated to produce TL (RERF, 1983). Stimulation of light from materials using both thermal and light stimulation is in use worldwide in geologic studies to assist in the dating of events and materials (Godfrey-Smith and Pass, 1997). Development of a useful technology will require identification of common items carried by people that can serve as fortuitous dosimeters, determination of which have the sensitivity to be of use in post-exposure injury assessment, and development of realistic con-ops for readout and calibration.

The phenomenon of TL was first observed in diamond by Robert Boyle, who reported to the Royal Society in London on October 28, 1663 (Becker, 1975). Diamond films made using the chemical vapor deposition process, with various impurities to enhance radiation response, have been studied and shown to be effective dosimeter materials for radiation doses from 0.8 Gy to 3 kGy using OSL analysis (Barboza-Flores et al, 2004). Natural diamond has its own impurities (responsible for color and other qualities), and the radiation sensitivity for a particular gemstone would be determined a posteriori as part of the dosimetric analysis, as noted above. A variety of other minerals can be used for radiation dosimetry, including some semi-precious gems like sphene and epidote. The fundamental TL properties of these minerals have been studied at very high doses (1 - 3 kGy), but the range of radiation sensitivities needs to be determined (Khalifa, Khalifa and Durrani, 1986).

Natural quartz and its man-made analog used extensively in optical fibers provide another source of fortuitous dosimeters, both for evaluating radiation doses to incident victims and for establishing radiation isodose curves in the area surrounding a radiological event. Natural quartz is ubiquitous in nature and can be found virtually wherever there is dirt. Grains of sand from shoe soles, pants cuffs and pockets, city streets, and plant leaves provide a record of dose from a radiological event (Khan and Delincée, 1995). Fiber-optic strands are excellent radiation dosimeters from 0.1 Gy to several kGy and are associated with computer networks and cable service in many buildings (Espinosa et al, 2004). Optical fibers will probably be available for analysis of a radiological event, since such events are most likely to occur in areas with a highly developed infrastructure, either because of commercial use of the material involved in the event, or because of terrorist targeting.

Common table salt is also an excellent radiation dosimeter. Impurities such as potassium, calcium, magnesium, iron, copper and silver create defects in the salt crystal structure that provide sites where orbital electrons promoted by interaction with ionizing radiation become trapped and can be measured by EPR, TL or OSL. Radiation doses from 0.01 - 1,000 Gy have been

measured using untreated table salt (Kaibao et al, 1986). Any building with a cafeteria or break area, food vendors on the street and packages of salted snacks from the vicinity of a radiological event provide a wealth of material for radiation dosimetry.

The measurement and characterization of α particles from dispersion of uranium or transuranic materials, or neutrons from detonation of a nuclear device, is possible using a variety of glass or plastic materials, including picture glass, eyeglass lenses, and compact disks (Fleischer, 2002). Neutrons interact with uranium impurities in glass, causing them to fission and leave tracks (damage in the glass structure from energetic charged particles released in the fission event) that can be developed to visible size and counted. Polymer chains that make up plastic materials are damaged by charged particles from alpha emitters on the surface or from neutron interactions with atoms in the plastic itself. These can be etched with a caustic solution to 'grow' the damage sites to visible size. The number of damage sites reflects the total particle fluence (source strength), and certain characteristics of the tracks' geometry can be used to provide energy spectra, useful in identifying the source material (Phillips et al, 2004) and for estimating dose.

Optical Stimulation Instrumentation

Several OSL instrumentation systems currently exist, some of which are commercially available. (Bøetter-Jensen et al., 2003). All current commercial systems, however, are designed for bench-top use only; none are portable. Most extensively used are those systems designed for automated, multiple-sample analysis, primarily for geological or archaeological dating (e.g. those systems manufactured by Riso National Laboratory or by Daybreak Inc). Others are designed for personnel dosimetry application, such as the InLight™ system manufactured by Landauer Inc. All of these systems, however, are designed to have the sample (or dosimeter) placed inside the apparatus and none is appropriate for the current application. Polf et al. (2004) and Gaza et al. (2004) describe a fiber-optic system designed to measure absorbed doses by Al_2O_3:C OSL dosimeters. Overall design is based on similar systems described earlier by Justus et al. (1999) and Huston et al. (2001). Similar apparatus is also described by Anderson et al. (2003). The primary application for each of these systems is *in-vivo* radiation dosimetry during radiotherapy (external beam and/or brachytherapy) and the OSL measurement scheme in these applications is by continuous-wave stimulation (CW-OSL). A similar system is described by Klein et al (2004) for environmental dosimetry. Since the goal of the latter work is to measure low level environmental doses the Klein et al. apparatus is designed for optimum sensitivity, and uses pulsed OSL (POSL) rather than CW-OSL. POSL measures the OSL signal between stimulation pulses rather than during the stimulation and leads to a high signal-to-noise ratio.

Electron Paramagnetic Resonance

The development of the theory and instrumentation of electron spin resonance paralleled that of TL and OSL. ESR (also called EPR, electron paramagnetic resonance) has made it possible to detect radiation doses absorbed by a very wide variety of organic as well as inorganic materials. The inorganic hydroxyapatite component of tooth enamel and bone is not only a well known natural dosimeter, it is also unique amongst all living tissues in its ability to retain the signal from absorbed radiation dose on time scales that are sufficiently long to be of geological significance. (Other tissues such as blood provide evidence of radiation exposure, but suffer from a rapid disappearance of detectable changes from absorbed dose.) For this reason, attempts to develop instrumentation for *in vivo* ESR measurement of dose to teeth in humans have been recognized as a worthwhile goal (Ikeya and Ishii, 1989; Yamanaka et al., 1993). Unfortunately, these early efforts resulted in microwave burns to volunteers. Although progress is being made in this regard, most recently reported data indicate that applications to human teeth

are still at the *ex vivo* stage, although the instrumentation is suitable for *in vivo* applications with research animals (Miyake et al., 2000; Swartz et al., 2004a, 2004b).

Further emerging development work, using smaller magnetic fields (smaller magnet systems) and lower frequencies, could lead to practical and safe *in vivo* dose assessment in teeth and bone. The goal would be to develop a portable instrument to rapidly assess clinically significant exposures in the field.

Ultrasound

Medical injury from a terrorist event (IND, RDD) is likely to involve thermal trauma in addition to radiation injury (combined injury). A high frequency ultrasound technique has been developed to function as a clinical tool to distinguish partial-thickness from full-thickness thermal burns (Roswell, Goans and Cantrell, 1977; Goans, Cantrell and Meyers, 1977; Cantrell, Goans and Roswell, 1978; Goans and Cantrell, 1978). Electrical and thermal burns represent a class of traumatic injury whose severity is difficult to diagnose through conventional clinical techniques. In many cases involving burns, the prognosis for patient survival is dependent upon an early and precise knowledge of both the magnitude of injury and of the depth of burn. This technique could be extended to analyze radiation-induced injury. The method is intended to use a conventional off-the-shelve medical ultrasound unit with an adjunct computer-driven analyzer.

Because most hospitals utilize ultrasound routinely, the potential use of ultrasound to estimate dose also has significant merit as an adjunct to fortuitous dosimeters (discussed above) or possibly internal dose estimates based on nasal swabs, among others. The concept has been proven in principle by its ability to evaluate burn damage (Goans and Cantrell, 1978). Like fortuitous dosimeters, that may be readable with readily available equipment, ultrasound analysis may also provide invaluable assistance in the identification of people who have received radiation exposures that were below a level with internally detectable dosage signals. This is of great importance if many people are assumed to be significantly exposed and medical triage must be administered.

A conventional ultrasound pulse-echo unit (5-30 mHz) was modified so that necrotic tissue at shallow depths (< 5 mm) from the skin surface could be resolved. Resolution of soft-tissue damage is less than 0.2 mm. This requirement was necessary so that deep dermal damage could be separated from epidermal necrosis and from thermal injury near the subcutaneous fat layer. The technique received a patent through the Oak Ridge National Laboratory and the Atomic Energy Commission (AEC) and was subsequently licensed into the private sector (Goans et al, 1978) where the technique has matured with improvement in ultrasound technology (Adams, Murphy, Gillespie and Roberts, 2000; Bauer and Sauer, 1989). The use of pulse-echo ultrasound is a stable clinical technique for ascertaining burn depth (Goans 1985). In that report, data were presented that show that the depth of necrotic tissue remains constant with time during a 12 day period after the burn was initiated.

Two pilot studies indicate that both pulse-echo ultrasound and standard B-scan ultrasonic imaging are sensitive to high-level radiation-induced cutaneous damage (Goans, 2005). Ultrasonic analysis of radiation burns appears to be much more complicated than for thermal burns because what is likely being measured is early vascular damage and vascular leakage. However, the sensitivity of the technique for measuring pathology is at least as great for radiation injury as for thermal injury. In fact, it may actually be more sensitive. Statistically significant changes ($p < 0.05$) in the magnitude of the reflected ultrasound spectrum have been noted less than 30 min post-irradiation.

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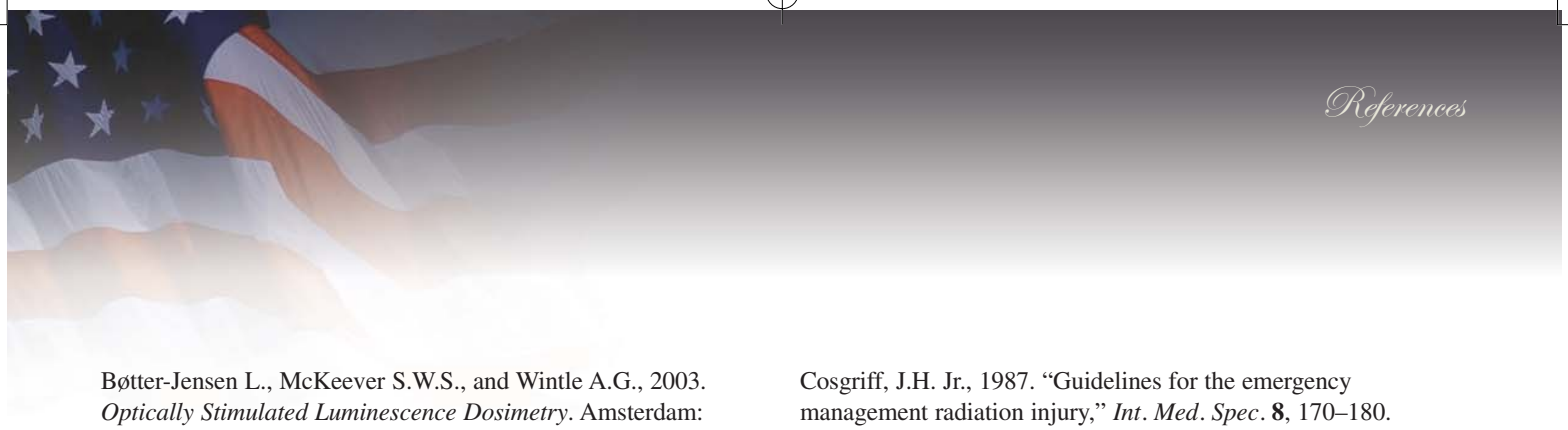

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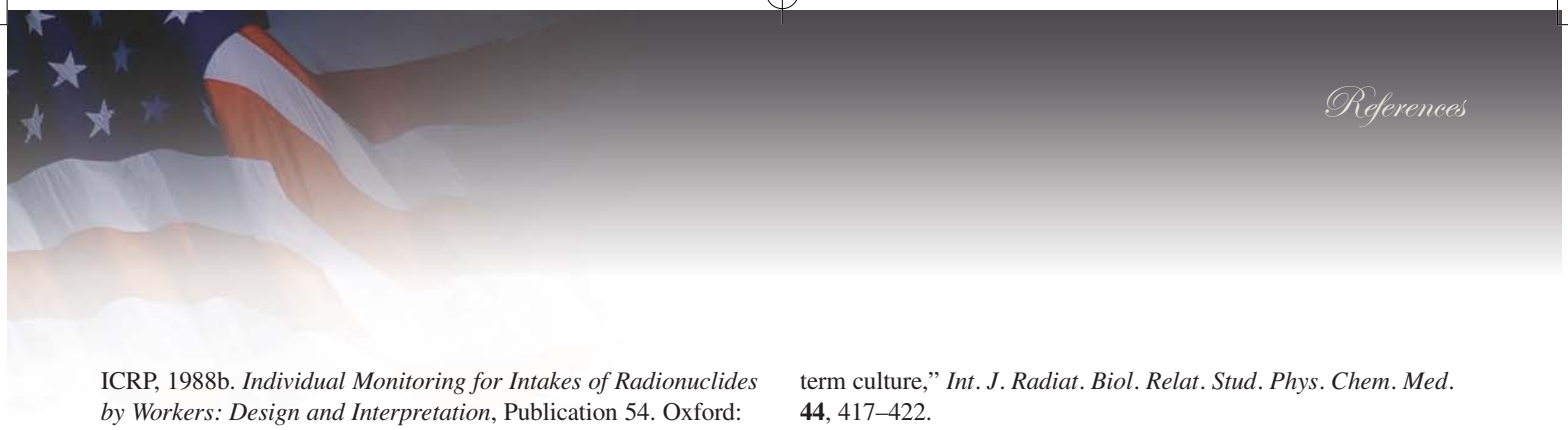

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Appendix A

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Appendix B

Abbreviations

AEC	Atomic Energy Commission
cGy	0.1 gray
COS	Commercial Off-the-Shelf
CPS	counts per second
DNA	deoxyribonucleic acid
EPR/ESR	electron paramagnetic resonance
FISH	Fluorescence *In Situ* Hybridization
Gy	Gray
HHA	handheld device
IAEA	International Atomic Energy Agency
IND	Improvised Nuclear Device
IR	Ionizing Radiation
ISO	International Organization for Standardization
JIWG	Joint Interagency Working Group
LFD	Lateral Flow Device
LIMS	Laboratory Information Management Systems
mRNA	messenger ribonucleic acid
OSL	Optically Stimulated Luminescence
PCC	Premature Chromosome Condensation
PCR	Polymerase Chain Reaction
REAC/TS	Radiation Emergency Assistance Center/Training Site
RDD	Radioactive Dispersal Device
RL	Radio Luminescence
R/N	Radiological and nuclear
SAGE	Serial Analysis of Gene Expression
SIRAD™	Self-Indicating Instant Radiation Alert Dosimeter
S/N	signl-to-noise
TL	Thermo Luminescence