Published in final edited form as:
Health Phys. 2012 September ; 103(3): 255–267. doi:10.1097/HP.0b013e3182588d92.

ELECTRON PARAMAGNETIC RESONANCE DOSIMETRY FOR A LARGE-SCALE RADIATION INCIDENT

Harold M. Swartz[*], **Ann Barry Flood**[*], **Benjamin B. Williams**[*], **Ruhong Dong**[*], **Steven G. Swarts**[†], **Xiaoming He**[*], **Oleg Grinberg**[*], **Jason Sidabras**[‡], **Eugene Demidenko**[*], **Jiang Gui**[*], **David J. Gladstone**[*], **Lesley A. Jarvis**[*], **Maciej M. Kmiec**[*], **Kyo Kobayashi**[*], **Piotr N. Lesniewski**[*], **Stephen D.P. Marsh**[†], **Thomas P. Matthews**[§], **Roberto J. Nicolalde**[*], **Patrick M. Pennington**[*], **Timothy Raynolds**[*], **Ildar Salikhov**[*], **Dean E. Wilcox**[**], and **Bassem I. Zaki**[*]

[*]Dartmouth Medical School, Hanover, NH 03755

[†]University of Florida, Gainesville, FL 32610

[‡]Medical College of Wisconsin, Milwaukee, WI 53226

[§]Washington University, St. Louis, MO 63130

[**]Dartmouth College, Hanover, NH 03755

Abstract

With possibilities for radiation terrorism and intensified concerns about nuclear accidents since the recent Fukushima Daiichi event, the potential exposure of large numbers of individuals to radiation that could lead to acute clinical effects has become a major concern. For the medical community to cope with such an event and avoid overwhelming the medical care system, it is essential to identify not only individuals who have received clinically significant exposures and need medical intervention but also those who do not need treatment. The ability of electron paramagnetic resonance to measure radiation-induced paramagnetic species, which persist in certain tissues (e.g., teeth, fingernails, toenails, bone, and hair), has led this technique to become a prominent method for screening significantly exposed individuals. Although the technical requirements needed to develop this method for effective application in a radiation event are daunting, remarkable progress has been made. In collaboration with General Electric, and through funding committed by the Biomedical Advanced Research and Development Authority, electron paramagnetic resonance tooth dosimetry of the upper incisors is being developed to become a Food and Drug Administration-approved and manufacturable device designed to carry out triage for a threshold dose of 2 Gy. Significant progress has also been made in the development of electron paramagnetic resonance nail dosimetry based on measurements of nails in situ under point-of-care conditions, and in the near future this may become a second field-ready technique. Based on recent progress in measurements of nail clippings, we anticipate that this technique may be implementable at remotely located laboratories to provide additional information when the measurements of dose on site need to be supplemented. We conclude that electron paramagnetic resonance dosimetry is likely to be a useful part of triage for a large-scale radiation incident.

Corresponding Author: Harold M. Swartz, MD, PhD, Dartmouth Medical School, HB 7785, Hanover, NH, 03755, Phone: 603-650-1955, Fax: 603-650-1717, Harold.M.Swartz@Dartmouth.edu.

Conflicts of Interest:
We have no conflicts of interest to declare.

Keywords

electron paramagnetic resonance dosimetry; in vivo tooth dosimetry; in vivo nail dosimetry; ex vivo nail dosimetry

INTRODUCTION

This paper provides an overview and up-to-date status report of the use of electron paramagnetic resonance (EPR) dosimetry for large-scale radiation events. After reviewing the context for which the technique is needed, this paper details three complimentary EPR dosimetry approaches—in vivo tooth dosimetry, in vivo nail dosimetry, and in vitro (ex vivo) nail dosimetry. These approaches vary somewhat in their utilities for dosimetry but are based on the same general phenomena: (1) ionizing radiation generates unpaired electrons (usually free radicals) in proportion to the absorbed dose; (2) EPR can selectively and sensitively detect and quantify the number of unpaired electrons; (3) in some tissues (e.g., teeth, nails, and bone) these free radicals are sufficiently stable to be measured by EPR long after irradiation (from weeks to years).

When a large number of people are potentially exposed to ionizing radiation, an adequate medical and social response requires the capability to distinguish between those who are significantly exposed from those who are not exposed to levels of radiation that could lead to acute radiation syndrome (ARS) (Buddemeier and Dillion 2009; Gougelet et al. 2010; Grace et al. 2010; Waselenko et al. 2004). Two gray (Gy) is the generally accepted threshold dose to identify those individuals whose level of exposure is sufficiently predictive of ARS to warrant medical intervention (Demidenko et al. 2009; DiCarlo et al. 2011; Grace et al. 2010; Rea et al. 2010). Following an initial screening to identify individuals who need immediate medical attention, more refined assessments of the absorbed dose, possibly coupled with information about the patient's biological reactions to radiation, can help direct effective clinical management (Coleman et al. 2009; Flood et al. 2011; Grace et al. 2010).

A challenge to meeting the need for estimating exposure dose and assessing medical response, especially in a mass casualty event, is that the current guidelines for deciding if an individual should enter the health care system after a large radiation event are inadequate for making informed and timely decisions under such circumstances (Swartz et al. 2010; Swartz et al. 2011). While some recommended methods (e.g., dicentric chromosome assay and lymphocyte depletion rate) have demonstrated their usefulness for the clinical management of exposed individuals in small events, these methods cannot be effectively employed when many thousands of people must be evaluated and medical decisions made quickly (Flood et al. 2011; Gougelet et al. 2010; Parker and Parker 2007; Romm et al. 2011). In particular, methods that require sample analysis at a remote laboratory may be ineffective after a radiation incident because transporting samples and later matching the results with the correct individuals could prove difficult in chaotic conditions. Other frequently proposed approaches for triage, such as time to emesis and clinical signs and symptoms, do not provide sufficient dose resolution to be suitable in a large-scale radiation event (Demidenko et al. 2009).

New methods are needed to estimate the dose for large events, and biodosimetry will likely play an important role in such determinations (Swartz et al. 2010; Flood et al. 2011). Biodosimetry does not rely on a person being in close proximity to a conventional dosimeter at the time of the event or having an external dosimeter based on commonly carried objects, such as credit cards or cell phones. Instead, it uses each individual's own tissues and their

response to ionizing radiation, thereby assuring that the material for dosimetry will always be there to absorb the dose and be measured.

The role of biodosimetry for triage of a large radiation exposure event

There is considerable interest and effort in the development of biodosimetry, and the National Institutes of Health (NIH) Center for Medical Countermeasures against Radiation (CMCR) program supports both biologically-based and physically-based biodosimetric methods. Biologically-based methods, such as changes in gene expression, protein levels, or metabolites (Brengues et al. 2010; Coy et al. 2011; Flood et al. 2011; Gougelet et al. 2010; Ossetrova et al. 2010; Rana et al. 2010), support clinical management by providing an indication of the biological implications of the dose, in addition to the dose itself. However, because these approaches are usually based on altered levels of normal response mechanisms and biomolecules, they are unlikely to be specific to ionizing radiation. This lack of specificity may be especially problematic in the context of a large radiation event in which stress and concurrent physical injuries are likely to be present, thereby confounding changes in the measurable parameters. Nevertheless, because more information should be available about potential confounding factors after the initial triage steps following a mass casualty event, biologically-based biodosimeters may be especially useful in guiding treatment when the number of individuals is small, their location is established, confounding factors can be determined, and immediate results are unnecessary (Swartz et al. 2010).

Physically-based biodosimeters, such as EPR and optically stimulated luminescence (OSL) (Ainsbury et al. 2011; Bassinet et al. 2010; DeWitt et al. 2010; Williams et al. 2011b), detect structural changes induced by radiation exposure and do not rely on the biological response to radiation. Consequently, they provide information only about the dose, not about the individual's specific reaction to radiation. However, because physically-based biodosimetry is not confounded by most pre-existing pathophysiology, concurrent stress, or wounds external to the site of measurement, it may be especially useful for the initial steps in triage where clinical management is not the primary goal. This first stage of triage determines if exposure is high enough to produce ARS and warrants further clinical evaluation of signs and symptoms of radiation exposure in a second stage of triage. While several physically-based techniques are being investigated, only EPR dosimetry has demonstrated significant promise of being suitable to effectively triage thousands of victims under field conditions (Swartz et al. 2007; Williams et al. 2011b).

The role of physically-based dosimetry using EPR

The dosimetry program at Dartmouth Medical School (Hanover, NH) focuses on EPR measurement of teeth and nails to determine radiation exposure. Its overarching aim is to produce a prototype of one or more dosimetry devices that meet the needs for effective and efficient triage after a large-scale radiation exposure event and can be operated by minimally trained personnel. Dartmouth's targeted end product is the design of a dosimetric system that a medical device company can use to manufacture FDA-approved instruments. In collaboration with General Electric (GE) and with support from the Biomedical Advanced Research and Development Authority (BARDA), Dartmouth is developing a prototype of one such device based on in vivo measurements of incisor (front) teeth.

EPR dosimetry has a number of characteristics that make it especially suitable for triage during large radiation exposure events (Swartz et al. 2007):

1. It is based on physical processes that are not confounded by most types of trauma and stress that are likely to occur in a major radiation exposure event unless there is direct major physical changes such as charring from heat, which should be readily apparent.

2. The measurable effect of radiation occurs instantaneously upon exposure, is independent of the rate of exposure, and reflects the cumulative dose.
3. The measurements can be made for a considerable time after the event during which triage and assessment would be pertinent (from immediately up to several weeks after exposure using nails and indefinitely using teeth) (Black and Swarts 2010; Desrosiers and Schauer 2001; Symons et al. 1995; Trompier et al. 2009).
4. Since the in vivo measurements are non-destructive, repeated measurements can be made as needed.
5. Measurements can be made at the site of the event (i.e., analysis at a distant laboratory is unnecessary), with immediate readout of the estimated dose (Williams et al 2011b). Measurements of nail clippings can be adapted for detailed analysis and archival storage at distant laboratories when the logistics of the situation make such analyses feasible.
6. With the exception of ex vivo analysis of nail samples that are obtained by simple clipping, measurements are noninvasive.
7. Measurements using teeth and nails from all four limbs can be used to compare estimates of the dose at multiple anatomical sites, thereby indicating whether exposure is homogeneous.
8. EPR dosimetric measurements can be made with throughput times of less than 6 minutes from measurement to results with devices operated on site that are currently being developed for operation by nonexpert personnel.
9. Because the method is based on physical changes, patients undergoing total body irradiation (TBI) are suitable test subjects, providing a means to test effectiveness directly in human subjects. Biologically-based biodosimetric techniques, on the other hand, can be confounded by diseases and treatments, such as chemotherapy; consequently, most tests must be done in animals.

Individual variations in factors such as tooth and nail anatomy, exposure of the tooth enamel to UV light, and nail hydration will contribute to variations in the EPR signal amplitudes and, therefore, variations in dose estimate. However, based on studies to date and the literature (Sholom et al. 2010), many of these variations are expected to be small for the purposes of ARS triage and efforts are underway to further minimize their effects.

Even with these efforts to optimize the performance of the physically-based biodosimetric techniques, there are some characteristics that are likely to limit their applicability in some situations:

1. They measure dose at the specific site that is measured (i.e., in the teeth or nails) and do not reflect the biological implications of the dose for the individual.
2. They provide only total cumulative dose over the period when the radicals interrogated are stable (which is indefinite for teeth and up to several weeks for nails). If there are prior exposures during this period, they will affect the observed signals in an additive manner. However, prior doses received substantially earlier may have little or no biological implications for current responses to damage. In this case, the currently received dose and subsequent responses would be overestimated.
3. While some of the EPR techniques have been shown to have sufficient resolution for initial triage, to date they have not been demonstrated to have sufficient dose resolution to guide medical treatment *after* the initial triage step.

4. Their application may not be feasible to measure all individuals. The in vivo tooth dosimeter requires the presence of a suitable tooth (e.g., without fillings or caries), and the ex vivo nail technique requires suitable nail length for clipping.

5. EPR tooth dosimetry does not directly measure dose from neutrons, because of the paucity of hydrogen nuclei in enamel. But if complementary measurements are available that are affected by neutrons and gamma, this potential limitation could become an advantage when both methods are used together, i.e., allowing differential determination of how much of the exposure was due to neutrons vs gamma radiation.

Physical biodosimetry based on EPR measurements of teeth *in vivo*

Of the three EPR dosimetric methods under development, dose estimation determined through tooth enamel measurements is the most mature (Fattibene and Callens 2010). Ex vivo EPR measurements at X-band of enamel extracted from isolated teeth are well accepted for retrospective dosimetry involving large populations for the assessment of the long-term effects of radiation. This technique has been used, for example, to assess populations exposed following the Chernobyl reactor accident, those with potential exposures from radiation releases due to weapons production and testing, and those with exposures due to the detonations at Nagasaki and Hiroshima (Ishii et al. 1990; Nakamura et al. 1998). In this ex vivo system, standard deviations in dose estimation can be as low as 20–30 mGy for individuals and 5 mGy from data averaged over large groups (Ivannikov et al. 2000). The development of these applications has significantly advanced our understanding of the value of teeth as dosimeters, although they are not suitable for addressing the unique challenges of rapidly screening a large population with heterogeneous exposures for identification of individuals likely to experience ARS (Flood et al. 2011; Swartz et al. 2011). The development of instrumentation and procedures that enable quantitative in vivo EPR measurements to be made with intact tooth enamel is likely to meet these challenges and enable assessment of thousands of individuals over the short period when treatment or mitigation must be initiated (Swartz et al. 2010, 2011; Williams et al. 2011a; Williams et al. 2011b).

We have produced and tested an operational prototype of a deployable L-band (1200 MHz) EPR tooth dosimeter (Fig. 1). This system, which utilizes a ~60-lb permanent dipole magnet with a 17-cm gap produced by Resonance Research, Inc. (Billerica, MA, USA), enables intact teeth in individual subjects to be measured through a completely noninvasive procedure. The electronics for EPR detection and magnetic-field sweeping are contained in a single deployable instrument rack that can be powered using the public electric supply or an electric generator. The system can be transported in two rugged Pelican-style boxes and put into operation in approximately 20 minutes; thereafter, individual measurements can be made in 6 minutes or less. This prototype is appropriate for use by expert or nonexpert operators trained through established measurement protocols. Under the contract from BARDA, there are ongoing developments to eliminate the need for any special expertise or training for the operator, and this system is being refined to include fully integrated software and hardware components to allow for full automation of all data acquisition procedures, including resonator positioning and spectrometer tuning.

In the current EPR tooth dosimetry system, subjects are seated with their head in a dipole magnet and positioned, with the help of a custom-made bite block, so that their upper incisor tooth is located within the central region of the homogeneous magnetic field. Following visual confirmation that the tooth is situated properly, an operator positions the sensing loop of an external loop resonator against the tooth surface. For each measurement, the detection loop is placed in a consistent standard position on the tooth surface, where the upper edge of

the loop is positioned approximately 1 mm below the gumline of the upper incisor tooth and the loop is centered horizontally with the tooth. The resonator is held in place during measurements with a lockable articulating arm and a spring-loaded holder that ensures close contact between the sensing loop and the tooth surface. Following brief manual tuning and matching procedures for the radio frequency (RF) detection system, EPR spectral data are collected for a period of approximately 60 seconds. This process is repeated for a total of 3–5 datasets, including tuning, coupling, and positioning of the resonator on the tooth to achieve independent spectral noise patterns which can be ameliorated via averaging (Williams et al. 2011b). The data from each of these sets are analyzed using non-linear least-squares fitting to estimate the amplitude of the radiation-induced signal (RIS), which are then averaged and then related to the absorbed dose via an empirically-based calibration curve. These calibration curves are specific for instrumental configurations and tooth types, and are based on in vivo measurements with unirradiated subjects and patients who have undergone total body irradiation procedures. Additional support of these calibration curves is provided by measurements made in anthropomorphic mouth model systems, which mimic in vivo RF conditions and incorporate natural human teeth.

Field deployment and in vivo measurements of unirradiated volunteers—The ability to use the tooth dosimeter in the field has been evaluated in a series of deployment exercises, including operation at a local firehouse, an international EPR conference, and three annual Dartmouth Cancer Center fundraisers held in tents (Fig. 2) (Nicolalde 2010; Williams et al. 2011b). Exercises to assess the field-deployment capabilities of EPR tooth dosimetry systems have been carried out over the last 3 years, marking the evolution of the tooth dosimeter from a fixed laboratory system to a rapidly deployable modular system.

The largest group measured to date was at the 2011 Dartmouth Cancer Center fundraiser, where 83 volunteers were measured. The exercise was conducted over a period of 12 hours using two L-band EPR tooth dosimetry systems, as described above and identical other than modest differences in the magnet support structure and level of automation of the RF bridge. Both systems were operated by experienced operators. Consistent with prior deployment exercises with similar manually controlled instrumentation, an overall throughput of approximately 15 minutes per subject was established (Nicolalde 2010). However, measurement procedures were not optimized for maximal throughput; they included serially performed procedures to educate volunteers prior to measurements, an average of 5.8 minutes of EPR data collection, and cleaning of the systems and replacement of disposable parts in between measurements. For each subject, EPR data were collected with adequate sensitivity for dose estimation, although the precision of these estimates was not as high as that currently acquired under laboratory conditions.

Aside from human factors and organizational optimizations, a major effort to streamline these operations via instrumental improvements to the L-band tooth dosimeter is underway through the contract from BARDA. This effort includes developments to increase detection sensitivity of the dedicated RF bridges and resonators and full automation of subject and resonator positioning and spectrometer operation.

In vivo measurements of radiation dose—The utility and performance of the tooth dosimetry system were tested through a series of measurements in a clinical setting with unirradiated subjects and patients who received TBI prior to bone marrow transplants (Williams et al. 2011a). Fig. 3 includes the results from a total of 37 sets of dosimetric spectra acquired for unirradiated subjects and TBI patients. The estimated RIS amplitudes were used to estimate an in vivo dose-response curve in which the EPR signal in volts was related to the known dose. This group included 15 unirradiated subjects (0 Gy), 1 patient who received a single fraction of 1.5 Gy, 8 patients who received a single fraction of 2 Gy,

and 2 patients who received fractionated TBI for a total dose of 12 Gy. As EPR measurements are nondestructive, and the signal is indefinitely stable, independent repeat measurements were performed for several of the unirradiated subjects and patients. These data demonstrate the linear dose response and the current level of variation observed in the collected data. The standard error of inverse predication (Draper and Smith 1998) based on these data is 1.2 Gy. For the 0, 2, and 12 Gy doses where multiple measurements with multiple subjects were acquired, the standard deviations of the RIS amplitudes appeared to be uniform across doses. This observation is consistent with the presence of an additive instrumental noise source that is not related to interpersonal variation in dose response.

Current and future efforts—In summary, EPR tooth dosimetry can discriminate dose levels for triage (i.e., 2 Gy) in less than 5 minutes of measurement time. The existing L-band EPR tooth dosimetry system is undergoing further refinements at Dartmouth in collaboration with GE and an international team of instrumental EPR experts via funding from BARDA. This effort focuses on measurements of the upper incisors; the refinement of instrumentation and procedures will improve the sensitivity and specificity of this technique and allow reliable use with nonexpert operators under field conditions through full and robust automation. We are working in close collaboration with colleagues at the Dana-Farber Cancer Institute (DFCI, Boston, MA) on a 5-year development plan that includes greatly expanded studies involving appropriate mouth-model systems and patients undergoing TBI to validate the technology and facilitate the application for approval by the FDA.

While the L-band system is currently the most mature technology for EPR tooth dosimetry and will be the first available for widespread use, alternative EPR detection strategies for tooth dosimetry may provide additional sensitivity that could be used to further increase throughput or to provide higher levels of precision. These advanced instrumental methods are being funded by NIAID and have the potential to make EPR tooth dosimetry capable of providing sufficiently refined estimates of dose; thus, the technique could be developed for medical management of ARS (e.g., increased frequency could enhance sensitivity). Alternatives based on higher frequency systems will require the design of appropriate high-field magnets and resonators suitable for in vivo measurement. Another alternative would use a pulsed-mode EPR system that could provide an increased ability to discriminate between radiation-induced EPR signals and low-level signals from radicals native to unirradiated teeth (Sato et al. 2007).

Through the rapid production of an FDA-approved L-band EPR tooth dosimeter and the development of advanced techniques that may offer additional sensitivity or increased throughput, EPR tooth dosimetry is poised to become an integral component of the response to a large-scale radiation exposure event.

Physical biodosimetry based on ex vivo EPR measurements in nails

The use of RIS in fingernails and toenails as a method for estimating an individual's radiation-exposure dose was first suggested by Brady et al. (1968) and Symons et al. (1995) in their early studies of irradiated nail clippings. Recently, there has been a concerted effort to assess if RIS in irradiated nails can be used to estimate exposure dose with the precision necessary for screening patients in a mass casualty radiological or nuclear event. Studies by Black and Swarts (2010), Reyes et al. (2008, 2009), Romanyukha et al. (2010), Swartz et al. (2007, 2010), Trompier et al. (2007, 2009), and Wilcox et al. (2010) show that nail clippings irradiated ex vivo generally exhibit linear dose dependence within the clinically relevant range of 0–10 Gy.

An important challenge to the development of ex vivo EPR nail biodosimetry is that when an individual's nail is clipped before EPR analysis, a mechanically-induced signal (MIS) is

superimposed on any RIS (Fig.4) (Black and Swarts, 2010; Reyes et al., 2008; Romanyukha et al., 2010; Swartz et al., 2007, 2010; Trompier et al., 2007; Wilcox et al., 2010). Mechanical scission of bonds in the keratin fibers and disulfide bridges gives rise to a combination of three distinct EPR signals that are thought to originate from three separate radical centers initially localized along the cut edge, thereby resulting in an MIS (Black and Swarts 2010; He et al. 2011; Wilcox et al. 2010). The presence of this MIS limits the ability to directly quantify the RIS in an irradiated nail clipping.

Approaches for removing the MIS—Methods have been developed to remove the interfering MIS. One method involves treating the nail clipping with water or a redox agent, such as thiols or ascorbic acid, to eliminate the radicals responsible for the MIS. This method takes advantage of an expected differential distribution of the radical centers, with MIS thought to be located predominantly along the cut edge and RIS distributed throughout the bulk of the nail clipping. Thus, a short exposure of the nail clipping to water or a redox agent is expected to preferentially affect the stability of the edge-localized MIS radicals, thereby eliminating the MIS and leaving the RIS. While these treatments have been assessed and shown to remove the MIS (Black and Swarts 2010; Romanyukha et al. 2007), they also result in decreased RIS. Although it may be possible to account for the effect of such a treatment on the RIS through carefully controlled conditions, other techniques that can selectively remove the interfering MIS without affecting the RIS are preferable.

One such approach involves selective removal of the spectral components of the multi-component MIS spectrum through spectral decomposition. This method has been tested for its ability to estimate the RIS in nail clippings irradiated to 0, 1, 2, 4, and 8 Gy (He et al. 2011). Reference spectra for the three spectral components that comprise the MIS (a singlet, a broad anisotropic signal, and a doublet) were acquired (Fig. 5), and a simple decomposition algorithm was used to subtract the MIS spectral components and measure the remaining RIS in the irradiated nail spectra (Fig. 6).

A test of this method showed the expected linear dose response for the RIS when the mean values of the measured RIS were plotted, as shown in Fig. 7 (He et al. 2011). An analysis of the group means of the RIS measurements resulted in a standard error of inverse prediction of 0.25 Gy (Draper and Smith 1998), When calculated on an individual basis, the SEP was found to be too high to provide the dose precision needed for triage. The variability in the RIS measurement was mainly due to the variability in the $MIS_{singlet}/MIS_{broad}$ ratio that was used to estimate the $MIS_{singlet}$ component of the composite MIS (Fig. 8). Because the magnitude of the $MIS_{singlet}$ cannot be directly determined, due to its superposition with the RIS, this ratio is required for the decomposition method. Therefore, the MIS_{broad} signal is used to estimate the $MIS_{singlet}$ by assuming a constant $MIS_{singlet}/MIS_{broad}$ ratio and similar stabilities of the two signals in clipped nails. However, Fig. 8 suggests that the ratio of the two signals is not constant after cutting, the stabilities of the two signals are not similar, or both.

Recent unpublished studies of the $MIS_{singlet}/MIS_{broad}$ ratio suggest that the key to accurate and reproducible spectral decomposition of MIS is controlling signal decay following harvest of the nail clipping. Since the stabilities of both the RIS and MIS spectral components depend on nail water content, MIS-component stability can be increased after the nail is harvested by rapidly reducing its water content after harvesting. These studies indicate that water and oxygen contents can be reduced by placing the nail clipping in a dry inert gas, such as carbon dioxide or nitrogen. Preliminary results show that by controlling the stability of the MIS spectral components using the modified nail sample handling method we are able to increase the correlation (Pearson) between the $MIS_{singlet}$ and MIS_{broad} to 0.93 from 0.68 that was achieved in the first dose-response trial described

above. This is a significant change ($P<0.02$) according to Wald test after a Fisher r to z transformation. Once the revised nail handling and decomposition methods achieve the desired precision in the dose estimate at the 2-Gy threshold, we will use the revised analytical methodology to analyze the RIS in clipped nails irradiated in vivo. Nail clippings for this study will be obtained from patients undergoing TBI in collaboration with Dr. Eva Guinan and her colleagues at DFCI.

Additional approaches for refining the analysis of the MIS and RIS—Ex vivo EPR nail biodosimetry to screen large numbers of samples will likely be done at remote sites, where conditions can be better controlled, avoiding artifacts from differences in handling due to variations in moisture, temperature, and other variables. In a remote setting, it will also be feasible to use more complex technical approaches, such as high-frequency EPR measurements and dose-additive methods. For example, Q-band (35 GHz) to enhance the spectral decomposition approach for removing the MIS is being evaluated. The work of Romanyukha et al. (2011) has shown an increased resolution of g-anisotropies in the RIS and $MIS_{singlet}$ spectra in the Q-band over that seen in the X-band spectra. This enhanced resolution of field-dependent spectral features may aid in discrimination of the two signals during spectral decomposition in the analysis of irradiated nail clippings. The potential of Q-band and other higher frequencies (e.g., W-band at 95 GHz) to assist in the analysis of RIS and MIS in freshly clipped nails is being investigated further.

The dose-additive method to calibrate the RIS in nail clippings is expected to provide further improvements in dose-estimate precision for ex vivo EPR dosimetry (Fig. 9). The effectiveness of this calibration technique will depend on further characterization of the dose response of RIS in nails, such as the dependence of the dose response on nail water content (Reyes et al. 2009). Because demographic variables (i.e., gender, age, and race) that result in changes in nail composition may also alter the dose response of the signal in nails, their potential confounding impact will be further investigated and modified techniques developed (i.e. alternative calibration schemes) to accommodate any changes in the dose-response that these factors may cause. The dose-additive method will likely require that the water content of the nail clipping be within a range that is representative of the distal extension of the whole nail when attached to the nail bed. This range will ensure that the dose response represented by the incremental changes of the RIS produced with each additive dose is similar to that of the dose-dependent response in vivo. With these improvements in spectral analysis, along with the efforts to refine the ex vivo irradiated nail model to simulate the in vivo situation, we anticipate that ex vivo EPR analysis of nail clippings will be developed into an effective biodosimetric method for retrospective dosimetry in mass casualty radiation exposure events.

Summary—EPR dosimetry of ex vivo nails has demonstrated excellent linearity of dose response over the desired range (0 to 10 Gy); however, as the variation among samples is greater than desired, further refinements of the technique are necessary. Recent results, summarized above, indicate that at least some of this variability is due to nail water content, as determined by the humidity at which the samples are held. If this hypothesis is correct, then it should be possible to control this source of variation sufficiently for ex vivo nails to be an excellent dosimeter for triage. We anticipate that clipped nails will be used to process a large number of samples at a remote site where steps, such as the dose-additive method and high-frequency EPR measurements, that overcome the variability among samples can be employed. This method could potentially be developed as a “home-kit” approach to dosimetry, where people could clip their own nails and send them to a lab for analysis.

Physical biodosimetry based on in vivo EPR measurements in nails

The measurement of the RIS in unclipped nails would provide several advantages. It would eliminate the MIS introduced by clipping, thereby bypassing any methods needed to separate RIS from MIS. Moreover, the necessary resources and personnel could easily be accommodated in field settings, paralleling the processes described for in vivo EPR for teeth (Fig. 10). Because this technique readily allows independent measurements to be taken at several body sites (i.e., both hands and feet), it could directly determine if an exposure was heterogeneous or homogeneous. Finally, as with in vivo EPR tooth dosimetry, results would be available immediately after the measurement and would not require further data processing.

Because the RIS in nails is expected to be lower than that found in tooth enamel, higher EPR frequencies (e.g., X-band at 9 GHz) than those commonly used to measure RIS in teeth (L-band) will be needed to obtain the detection sensitivity required for adapting the in vivo RIS measurements in nails as the basis for a biodosimeter. In contrast to nail clippings, which are low in water content, conventional higher frequency EPR techniques cannot be used in the presence of soft tissues, such as fingers or toes, because they absorb the microwave energy used to detect the RIS. Therefore, development of resonant microwave structures with electromagnetic fields shaped to penetrate into the nail but not into the tissue under the nail is a priority for in vivo nail measurements.

In collaboration with the National EPR Center at the Medical College of Wisconsin (Milwaukee, WI), Dartmouth has made considerable progress in developing such structures. At present, we have achieved sufficient sensitivity in model systems and soon will begin studies in human fingers using artificial nails. The latter studies will be done in collaboration with DFCI, using patient-volunteers undergoing TBI.

In vivo fingernail resonators—Using Ansoft's High Frequency Structure Simulator (HFSS, version 13), three structures have been optimized for in vivo biodosimetry using EPR techniques: a TE_{102} rectangular cavity with a sample aperture, a novel hemispherical TE_{121} resonator with a sample aperture, and a surface resonator array (Fig. 11). Previous studies (Ikeya and Ishii 1989; Ikeya et al. 1994) have used rectangular TE_{102} resonators for surface spectroscopy, but the other two configurations are novel structures for such measurements.

In our studies, the rectangular TE_{102} has shown promise as a surface-aperture resonator for use at X-band (9.5 GHz) for EPR in vivo spectroscopy (Fig. 11a). The surface resonator array (Fig. 11c) provides another promising geometry in which seven transmission-line resonators are placed in parallel positions to create a continuous and sensitive volume that samples only the nail and minimizes sampling of the underlying living tissues. Fig. 12 presents working models of the two resonators, including finger placement. In addition, we are considering a new resonator, the hemispherical TE_{121} cavity (Fig. 11b). This geometry is suitable for resonators using an aperture because the spherical θ index is the second wave number, where the magnetic field adds in the center of the resonator and produces two times the magnetic field of the rectangular TE_{102} equivalent magnetic field when the aperture is placed along the TE_{102} end wall. Simulations have been conducted on the surface aperture, surface array, and hemispherical resonator designs. Table 1 shows the calculated characteristics for each resonator. The saturable signal is defined as the maximum EPR signal intensity observed when each resonator is critically coupled with the sample. The power is adjusted so that the H_1 (i.e., the magnetic component of the microwave field) applied at the sample is constant between resonators, where the unsaturable signal is defined as the maximum EPR signal intensity observed when each resonator is critically coupled with a sample and the incident power is held constant between the resonators.

Specific absorption rate in vivo—One potential area of concern for the use of X-band frequency in vivo is heat deposition in the finger soft tissue. The acceptable amount of heat deposition is characterized by the specific absorption rate (SAR), which is the amount of power deposited into the tissue. The acceptable level of SAR for bodily extremities, such as fingers and toes, is 20 W kg^{-1}. We have calculated the expected SAR in the finger from the aperture resonators (Fig. 13) following the IEEE Specification Standard C95.3-2002 (Institute of Electrical and Electronics Engineers 2002) and using the established formula:

$$SAR = \frac{\int \sigma \left| \mathbf{E}^2 \right| \mathrm{dV}}{\rho}$$

where σ is the conductivity, E is the electric field over a given volume, and ρ is the material density. The density of muscle is 1.06 g mm^{-3}, as specified in Ansoft HFSS. Fig. 13 represents the data as a function of the aperture size of the resonator, showing that the aperture sizes that fit the geometry of the measured nail (5–6 mm) fall well within the set limits. Our direct measurements of SAR in suitable phantoms using a TE_{102} resonator (data not shown) demonstrated that the heating within the phantom was lower than that predicted in Fig. 13.

In a comparison between resonators, the apertures of the rectangular TE_{102} and hemispherical TE_{121} were adjusted until the SAR calculation was at 20 W kg^{-1}. Simulated signal intensity was obtained, and both saturable and unsaturable signals were plotted (Figs. 14a and 14b). No optimum signal intensity was found within a feasible range of aperture diameters. Surface resonator array (SRA)-calculated characteristics were determined at the same power level as the cavity resonators, and the resonator was moved away from the nail until a SAR of 20 W kg^{-1} was realized. Since there is no clear optimum signal, these simulations suggest that SAR and fingernail geometry are the limiting factors for the size of the apertures on the rectangular TE_{102} and hemispherical TE_{121} resonator. The SRA resonator has a clear optimum for the given geometry and is only limited by SAR. For all resonators there is a tradeoff between the distance of the active region to the sample versus the EPR signal intensity and given SAR measurement.

Summary—Three designs of in vivo nail resonators are being evaluated and appear to meet efficacy and safety requirements at their current stages of development. These designs are being optimized and tested in appropriate phantoms of fingers with nails. The next step will be to test these designs directly in human subjects, using normal volunteers and patients undergoing TBI. No insurmountable obstacles appear to block the implementation of this approach for effective dosimetry in the field.

CONCLUSIONS

In the event that large numbers of people are potentially exposed to levels of radiation that could lead to ARS, effective and rapid triage is essential. Existing guidelines, such as those provided by the International Atomic Energy Agency (2005) that make use of signs and symptoms, time to emesis and lymphocyte depletion rates, are unlikely to be effective in such circumstances. Physically- and biologically-based biodosimetry methods that can be conducted on-site, providing close to real-time dose estimates, may be the solution to filling the need for rapid and accurate retrospective dose estimation. In addition, biologically-based methods have the ability to provide information on biological responses to not only the radiation exposure but combined injuries as well. Because physically-based biodosimetry is much less likely than biologically-based biodosimetry to be confounded by acute factors (e.g., simultaneous physical injury and stress) or individual factors (e.g., variations related to

gender, age, diet, or health conditions), these physically-based methods, and more specifically EPR dosimetry, should prove successful during initial triage for estimating dose. In addition to having fewer or no confounding factors, EPR offers distinct advantages for large-scale triage. In particular, EPR measurements can be made any time after the exposure, the results are available immediately after the measurement, and the technique is suitable for automation.

Three different but complimentary applications of EPR dosimetry are under active development and appear to be quite promising. Tooth dosimetry, using the upper incisors, is poised to be developed into a practical deployable method. In vivo nail dosimetry is also likely to be field deployable. Dosimetry based on nail clippings may be a complementary method, providing the capability to process a large number of samples if both transportation of samples and connecting the results to the individual are feasible.

Acknowledgments

We gratefully acknowledge the technical help of Jean P. Lariviere, Irina Milyavskaya, Sergey V. Petryakov, Kevin M. Rychert, and Dmitriy S. Tipikin and the editing contributions of Kate Casey-Sawicki.

Sources of Funding:

The work reported here is supported by a grant from NIH/NIAID (U19AI091173: Dartmouth Physically-Based Biodosimetry Center for Medical Countermeasures Against Radiation) and a contract from BARDA (HHSO100201100024C: In Vivo Electron Paramagnetic Resonance [EPR] Tooth Dosimetry for Rapid Point-of-Care Diagnostic Assessment of Absorbed Dose).

REFERENCES

1. Ainsbury EA, Bakhanova E, Barquinero JF, Brai M, Chumak V, Correcher V, Darroudi F, Fattibene P, Gruel G, Guclu I, Horn S, Jaworska A, Kulka U, Lindholm C, Lloyd D, Longo A, Marrale M, Monteiro Gil O, Oestreicher U, Pajic J, Rakic B, Romm H, Trompier F, Veronese I, Voisin P, Vral A, Whitehouse CA, Wieser A, Woda C, Wojcik A, Rothkamm K. Review of retrospective dosimetry techniques for external ionizing radiation exposure. Radiat Prot Dosimetry. 2010 Dec 23. [Epub ahead of print].
2. Bassinet C, Trompier F, Clairand I. Radiation accident dosimetry on electronic components by OSL. Health Phys. 2010; 98(2):440. [PubMed: 20065718]
3. Black PJ, Swarts SG. Ex Vivo Analysis of Irradiated Fingernails: Chemical Yields and Properties of Radiation-Induced and Mechanically-Induced Radicals. Health Phys. 2010; 98:301–308. [PubMed: 20065698]
4. Brady JM, Aarestad NO, Swartz HM. In vivo dosimetry by electron spin resonance. Health Phys. 1968; 15:43–47. [PubMed: 4317533]
5. Brengues M, Paap B, Bittner M, Amundson S, Seligmann B, Korn R, Lenigk R, Zenhausern F. Biodosimetry on small blood volume using gene expression assay. Health Phys. 2010; 98(2):179. [PubMed: 20065681]
6. Buddemeier, BR.; Dillon, MB. Key Response Planning Factors for the Aftermath of Nuclear Terrorism. Berkeley, Calif: Livermore, CA: Lawrence Livermore National Laboratory (LLNL); 2009. LLNL-TR-410067
7. Coleman CN, Hrdina C, Bader JL, Norwood A, Hayhurst R, Forsha J, Yeskey K, Knebel A. Medical response to a radiologic/nuclear event: integrated plan from the Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services. Ann Emerg Med. 2009; 53(2):213–222. Epub 2008 Apr 3. [PubMed: 18387707]
8. Coy SL, Cheema AK, Tyburski JB, Laiakis EC, Collins SP, Fornace A Jr. Radiation metabolomics and its potential in biodosimetry. Int J Radiat Biol. 2011; 87(8):802–823. Epub 2011 Jun 22. [PubMed: 21692691]
9. Demidenko E, Williams BB, Swartz HM. Radiation dose prediction using data on time to emesis in the case of nuclear terrorism. Radiat Res. 2009; 171(3):310–319. [PubMed: 19267558]

10. Desrosiers M, Schauer DA. Electron paramagnetic resonance (EPR) biodosimetry. Nucl Instrum Meth B. 2001; 184:219–228.
11. DeWitt R, Klein DM, Yukihara EG, Simon SL, McKeever SWS. Optically stimulated luminescence (OSL) of tooth enamel and its potential use in post-radiation exposure triage. Health Phys. 2010; 98(2):432. [PubMed: 20065717]
12. DiCarlo AL, Maher C, Hick JL, Hanfling D, Dainiak N, Chao N, Bader JL, Coleman CN, Weinstock DM. Radiation injury after a nuclear detonation: medical consequences and the need for scarce resources allocation. Disaster Med Public Health Prep. 2011; 5(Suppl 1):S32–S44. [PubMed: 21402810]
13. Draper, NR.; Smith, H. Applied Regression Analysis. 3d ed. New York: Wiley; 1998.
14. Fattibene P, Callens F. EPR dosimetry with tooth enamel: A review. Appl Radiat Isot. 2010; 68(11):2033–2116. [PubMed: 20599388]
15. Flood AB, Nicolalde RJ, Demidenko E, Williams BB, Shapiro A, Wiley AL, Swartz HM. A framework for comparative evaluation of dosimetric methods to triage a large population following a radiological event. Radiat Meas. 2011; 46(9):916–922. [PubMed: 21949481]
16. Gougelet RM, Rea ME, Nicolalde RJ, Geiling JA, Swartz HM. The View From the Trenches: Part 1-Emergency Medical Response Plans and the Need for EPR Screening. Health Phys. 2010; 98(2): 118. [PubMed: 20065673]
17. Grace MB, Moyer BR, Prasher J, Cliffer KD, Ramakrishnan N, Kaminski J, Coleman CN, Manning RG, Maidment BW, Hatchett R. Rapid radiation dose assessment for radiological public health emergencies: roles of NIAID and BARDA. Health Phys. 2010; 98(2):172. [PubMed: 20065680]
18. He X, Gui J, Matthews TP, Williams BB, Swarts SG, Grinberg O, Sidabras J, Wilcox DE, Swartz HM. Advances towards using finger/toenail dosimetry to triage a large population after potential exposure to ionizing radiation. Radiat Meas. 2011; 46(9):882–887. [PubMed: 22125410]
19. Ikeya M, Yamamoto M, Ishii H. Nondestructive measurement of large objects with electron-paramagnetic-resonance - pottery, sculpture, and jewel ornament. Rev Sci Instr. 1994; 65:3670–3672.
20. Ikeya M, Ishii H. Atomic bomb and accident dosimetry with ESR: natural rocks and. Int J Rad Appl Instrum A. 1989; 40:1021–1027. [PubMed: 2559050]
21. Institute of Electrical and Electronics Engineers. IEEE recommended practice for measurements and computations of radio frequency electromagnetic fields with respect to human exposure to such fields,100 kHz-300 GHz. Piscataway, NJ: IEEE-SA; IEEE Standard C95.3-2002 (http://standards.ieee.org/findstds/standard/C95.3-2002.html)
22. International Atomic Energy Agency. Generic procedures for medical response during a nuclear or radiological emergency. Vienna: IAEA: EPR-Medical; 2005. (http://www-pub.iaea.org/MTCD/publications/PDF/EPR-MEDICAL-2005_web.pdf)
23. Ishii H, Ikeya M, Okano M. ESR dosimetry of teeth of residents close to Chernobyl reactor accident. J Nucl Sci Technol. 1990; 27(12):1153–1155.
24. Ivannikov AI, Skvortsov VG, Stepanenko VF, Tsyb AF, Khamidova LG, Tikunov DD. Tooth enamel EPR dosimetry: sources of errors and their correction. Appl Radiat Isot. 2000; 52(5):1291–1296. [PubMed: 10836445]
25. Nakamura N, Miyazawa C, Sawada S, Akiyama M, Awa A. A close correlation between electron spin resonance (ESR) dosimetry from tooth enamel and cytogenetic dosimetry from lymphocytes of Hiroshima atomic-bomb survivors. Int J Radiat Biol. 1998; 73(6):619–627. [PubMed: 9690680]
26. Nicolalde, RJ. A methodology for evaluating the development of new clinical emergency response technologies: Testing its validity using the case of electron paramagnetic resonance dosimetry. Hanover, NH: Dartmouth College; 2010.
27. Parker DD, Parker JC. Estimating radiation dose from time to emesis and lymphocyte depletion. Health Phys. 2007; 93(6):701–704. [PubMed: 17993851]
28. Ossetrova NI, Sandgren DJ, Gallego S, Blakely WF. Combined Approach of Hematological Biomarkers and Plasma Protein Saa for Improvement of Radiation Dose Assessment Triage in Biodosimetry Applications. Health Phys. 2010; 98(2):204. [PubMed: 20065684]

29. Rana S, Kumar R, Sultana S, Sharma RK. Radiation-induced biomarkers for the detection and assessment of absorbed radiation doses. J Pharm Bioallied Sci. 2010; 2(3):189–196. [PubMed: 21829314]
30. Rea ME, Gougelet RM, Nicolalde RJ, Geiling JA, Swartz HM. Proposed Triage Categories for Large-Scale Radiation Incidents Using High-Accuracy Biodosimetry Methods. Health Phys. 2010; 98(2):136. [PubMed: 20065675]
31. Reyes RA, Romanyukha A, Trompier F, Mitchell CA, Clairand I, De T, Benevides LA, Swartz HM. Electron paramagnetic resonance in human fingernails: the sponge model implication. Radiat Environ Biophys. 2008; 47:515–526. [PubMed: 18584193]
32. Reyes RA, Romanyukja A, Olsen C, Trompier F, Benevides LA. Electron paramagnetic resonance in irradiated fingernails: variability of dose dependence and possibilities of initial dose assessment. Radiat Environ Biophys. 2009; 48:295–310. 2009. [PubMed: 19521713]
33. Romanyukha A, Trompier F, LeBlanc B, Calas C, Clairand I, Mitchell CA, Smirniotopoulosa JG, Swartz HM. EPR dosimetry in chemically treated fingernails. Radiat Meas. 2007; 42:1110–1113. [PubMed: 18163159]
34. Romanyukha A, Reyes RA, Trompier F, Benevides LA. Fingernail dosimetry: current status and perspectives. Health Phys. 2010; 98:296–300. 2010. [PubMed: 20065697]
35. Romanyukha A, Trompier F, Reyes RA, Melanson MA. EPR measurements of fingernails in Q-band. Radiat Meas. 2011; 46:888–892.
36. Romm H, Wilkins RC, Coleman CN, Lillis-Hearne PK, Pellmar TC, Livingston GK, Awa AA, Jenkins MS, Yoshida MA, Oestreicher U, Prasanna PG. Biological dosimetry by the triage dicentric chromosome assay: potential implications for treatment of acute radiation syndrome in radiological mass casualties. Radiat Res. 2011; 175(3):397–404. [PubMed: 21388284]
37. Sato H, Filas BA, Eaton SS, Eaton GR, Romanyukha AA, Hayes R, Rossi AM. Electron spin relaxation of radicals in irradiated tooth enamel and synthetic hydroxyapatite. Radiat Meas. 2007; 42:997–1004.
38. Sholom S, Desrosiers M, Chumak V, Luckyanov N, Simon SL, Bouville A. UV effects in tooth enamel and their possible application in EPR dosimetry with front teeth. Health Phys. 2010; 98(2): 360–368. [PubMed: 20065706]
39. Swartz HM, Burke G, Coey M, Demidenko E, Dong R, Grinberg O, Hilton J, Iwasaki A, Lesniewski P, Kmiec M, Lo K, Javier Nicolalde R, Ruuge A, Sakata Y, Sucheta A, Walczak T, Williams BB, Mitchell CA, Romanyukha A, Schauer DA. In vivo EPR for dosimetry. Radiat Meas. 2007; 42(6–7):1075–1084. [PubMed: 18591988]
40. Swartz HM, Flood AB, Gougelet RM, Nicolalde RJ, Rea ME, Williams BB. Implementing biodosimetry methods for large scale incidents. Health Phys. 2010; 98(2):95–10. [PubMed: 20065671]
41. Swartz HM, Williams BB, Nicolalde RJ, Demidenko E, Flood AB. Overview of biodosimetry for management of unplanned exposures to ionizing radiation. Radiat Meas. 2011; 46:742–748.
42. Symons MC, Chandra H, Wyatt JL. Electron paramagnetic resonance spectra of irradiated fingernails: a possible measure of accidental exposure. Radiat Prot Dosim. 1995; 58:11–15.
43. Trompier F, Romanyukha A, Kornak L, Calas C, LeBlanc B, Mitchell C, Swartz H, Clairand I. Electron paramagnetic resonance radiation dosimetry in fingernails. Radiat Meas. 2009; 44:6–10.
44. Trompier F, Kornak L, Calas C, Romanyukha A, LeBlanc B, Mitchell CA, Swartz HM, Clairand I. Protocol for emergency EPR dosimetry in fingernails. Radiat Meas. 2007; 42:1085–1088. [PubMed: 18163158]
45. Waselenko JK, MacVittie TJ, Blakely WF, Pesik N, Wiley AL, Dickerson WE, Tsu H, Confer DL, Coleman CN, Seed T, Lowry P, Armitage JO, Dainiak N. Strategic National Stockpile Radiation Working Group. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann Intern Med. 2004; 140(12):1037–1051. [PubMed: 15197022]
46. Wilcox DE, He X, Gui J, Ruuge AE, Li H, Williams BB, Swartz HM. Dosimetry based on EPR spectral analysis of fingernail clippings. Health Phys. 2010; 98:309–317. [PubMed: 20065699]
47. Williams BB, Dong R, Nicolalde RJ, Matthews TP, Gladstone DJ, Demidenko E, Zaki BI, Salikhov IK, Lesniewski PN, Swartz HM. Physically-based biodosimetry using in vivo EPR of

teeth in patients undergoing total body irradiation. Int J Radiat Biol. 2011a; 87(8):766–775. [PubMed: 21696339]

48. Williams BB, Dong R, Flood AB, Grinberg O, Kmiec M, Lesniewski PN, Matthews TP, Nicolalde RJ, Raynolds T, Salikhov I, Swartz HM. A deployable in vivo EPR tooth dosimeter for triage after a radiation event involving large populations. Radiat Meas. 2011b; 46(9):772–777. [PubMed: 21966241]

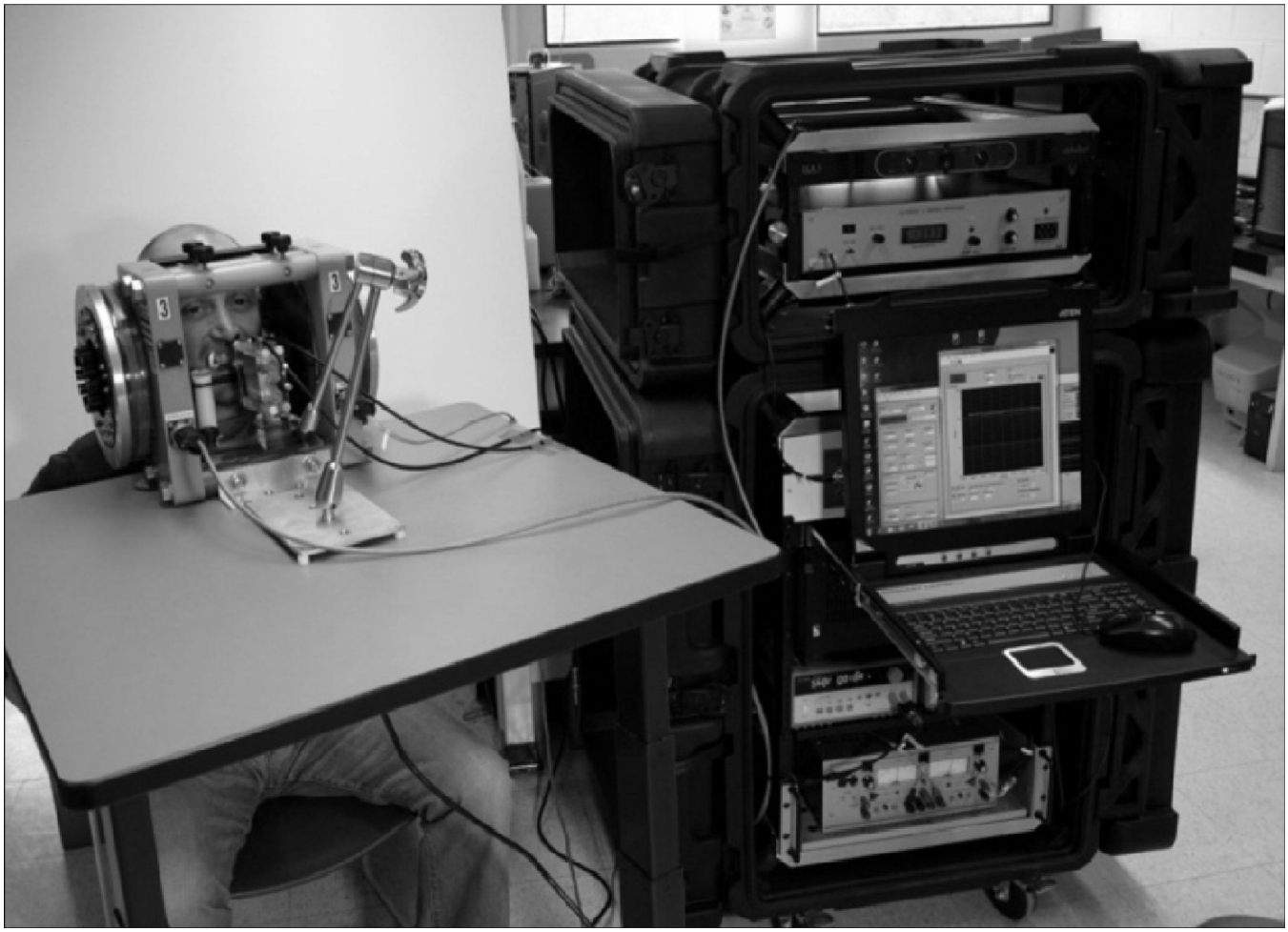

Fig. 1.
The existing deployable EPR tooth dosimeter includes self-contained, compact electronics, a display unit, and a 60-lb permanent magnet.

Fig. 2.
The prototype EPR tooth dosimetry systems have been operated successfully in field conditions, including measurements of walk-up volunteers at a local cancer fundraiser. Measurements were performed within a tent and a truck using power supplied by a remote generator.

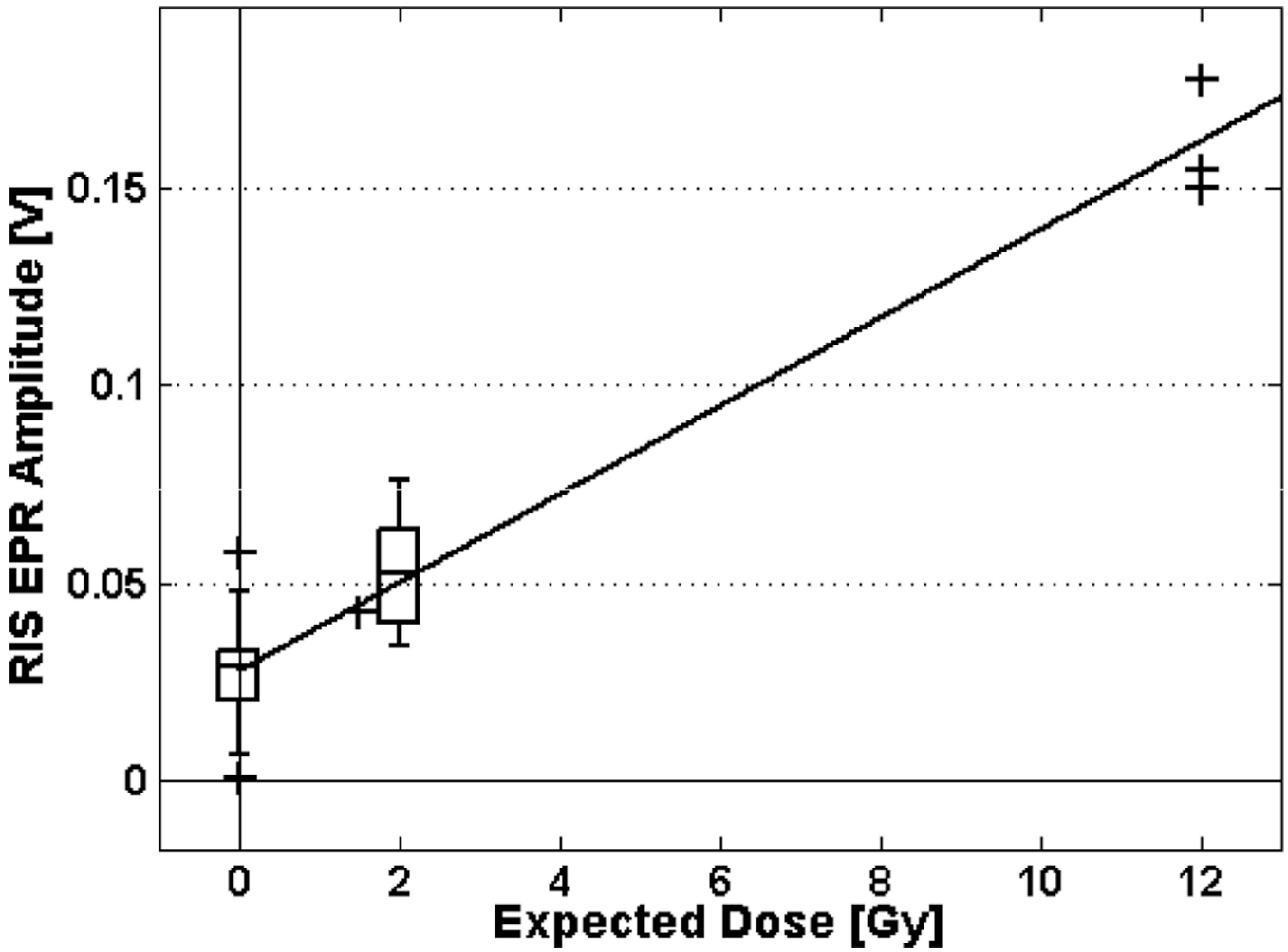

Fig. 3.

The dose response for the front surfaces of upper incisor teeth measured in vivo with the existing prototype tooth dosimeter. The distribution of EPR amplitudes for the radiation induced signal (RIS) is shown, where for 0-Gy and 2-Gy teeth the boxes show the 25% and 75% quartiles and the line in the box represents the median. The whiskers show the extent of data outside the quartiles. The "+" symbols identify measured values at other doses and a pair of 0 Gy outliers.

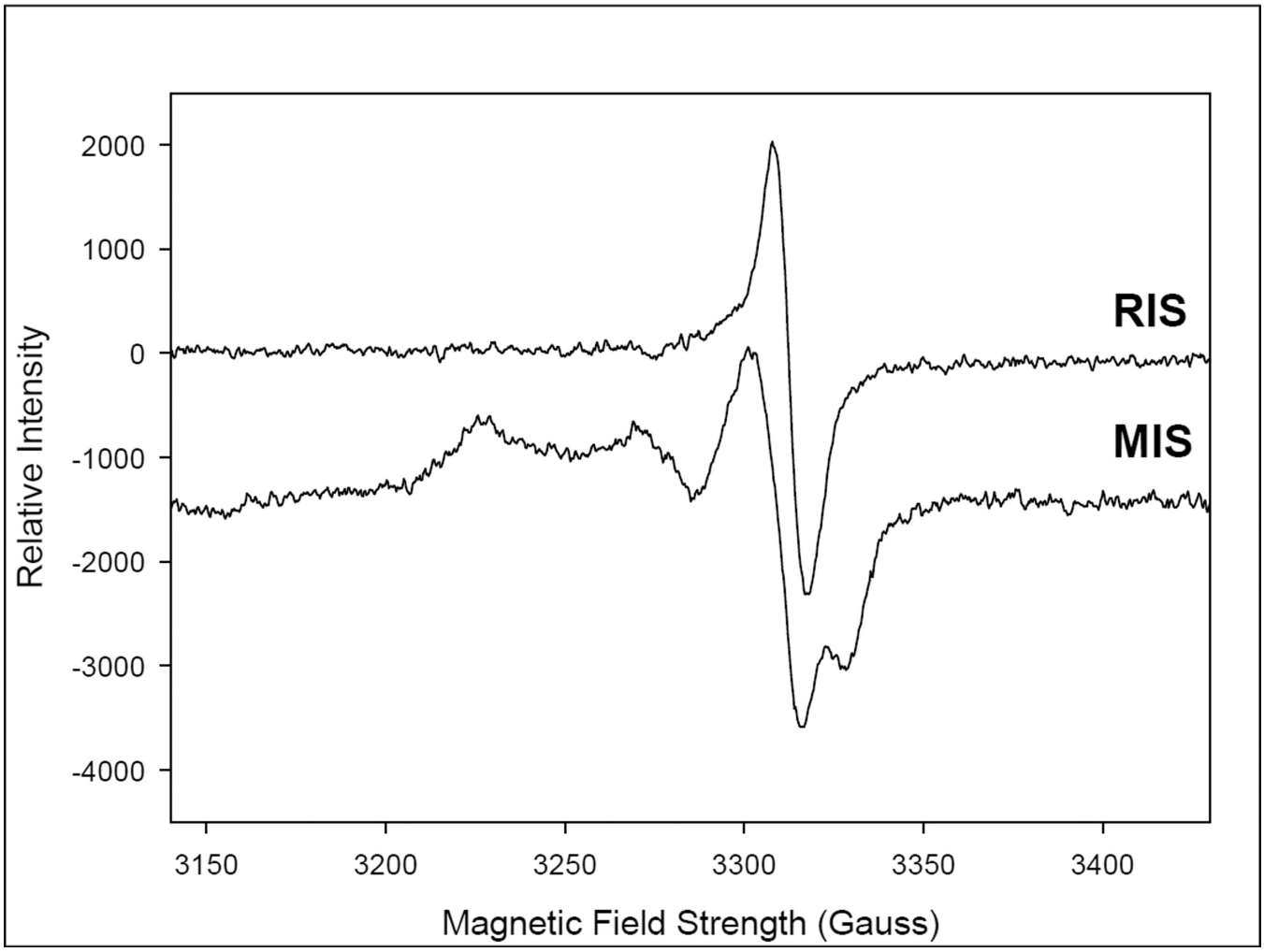

Fig. 4.
RIS and MIS spectra obtained from irradiated and unirradiated fingernail clippings, respectively. The RIS was obtained after 30 Gy was delivered to the clipping following a presoak of the nail in water for 15 minutes to remove the MIS and then 30 minutes of drying in the air prior to irradiation.

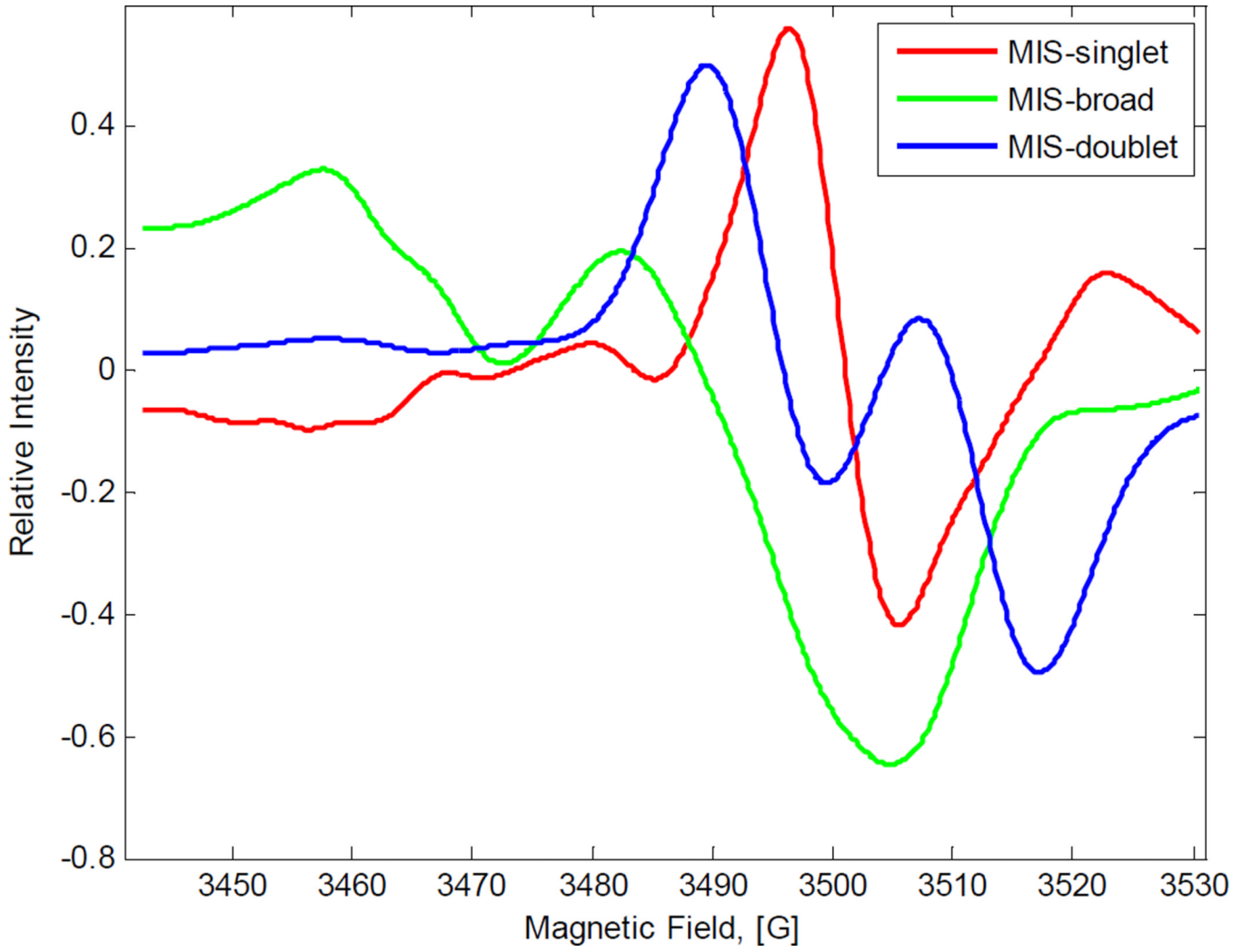

Fig. 5.
Reference spectra for the three MIS spectral components: $MIS_{singlet}$ (red), MIS_{broad} (green) and $MIS_{doublet}$ (blue).

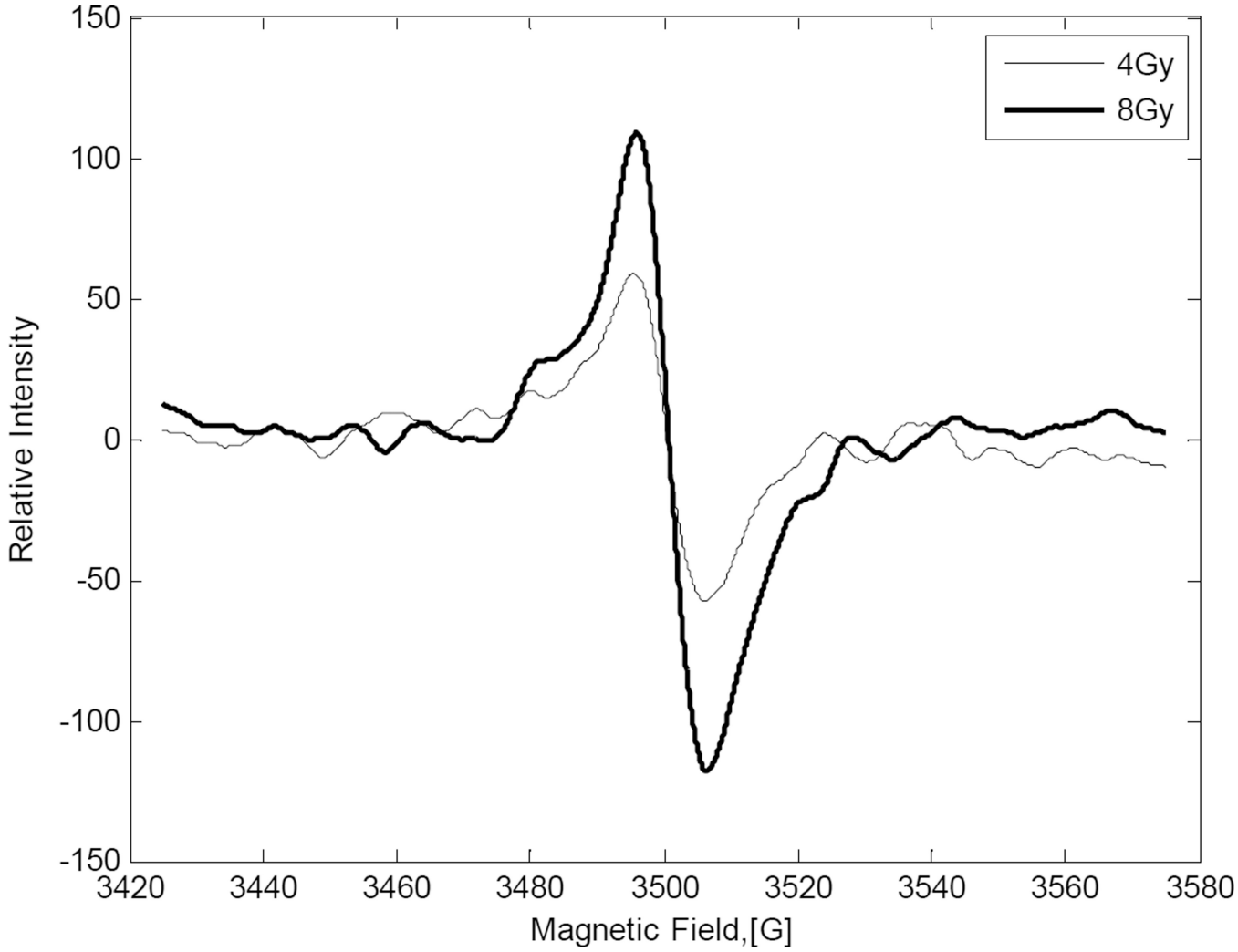

Fig. 6.
The RIS spectra obtained by use of simple spectral decomposition to remove the MIS in clipped nails irradiated ex vivo to doses of 4 Gy (thin line) and 8 Gy (bold line).

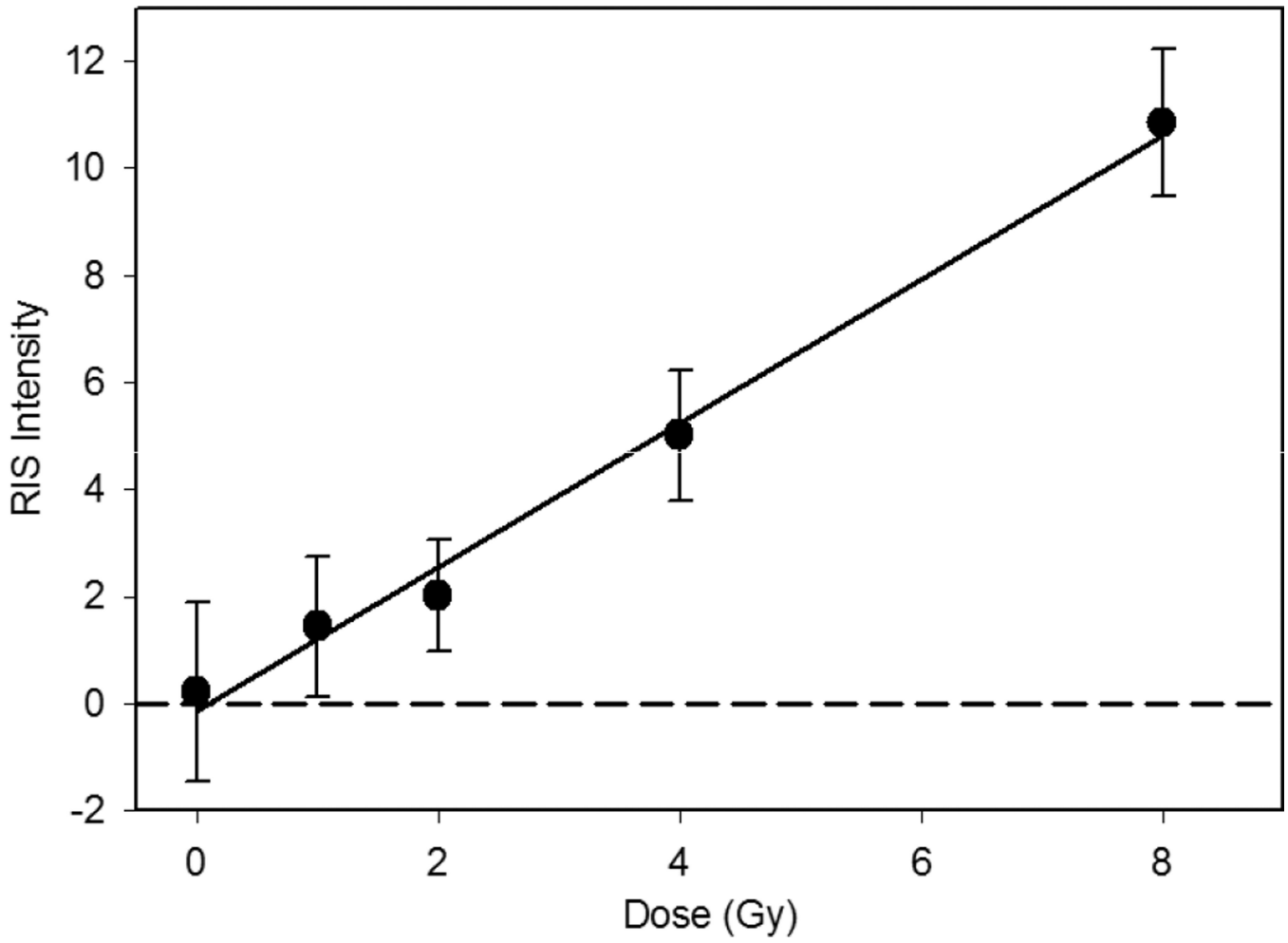

Fig. 7.

Plot of the intensity of the extracted RIS as a function of dose using a spectral decomposition method for the analysis of ex vivo irradiated nail clippings. The points represent the mean (± 1 SEM) nail clippings obtained from 20 volunteers. The line represents the linear regression analysis of the means:

$$y = 1.364x - 0.122,\ r^2 = 0.992.$$

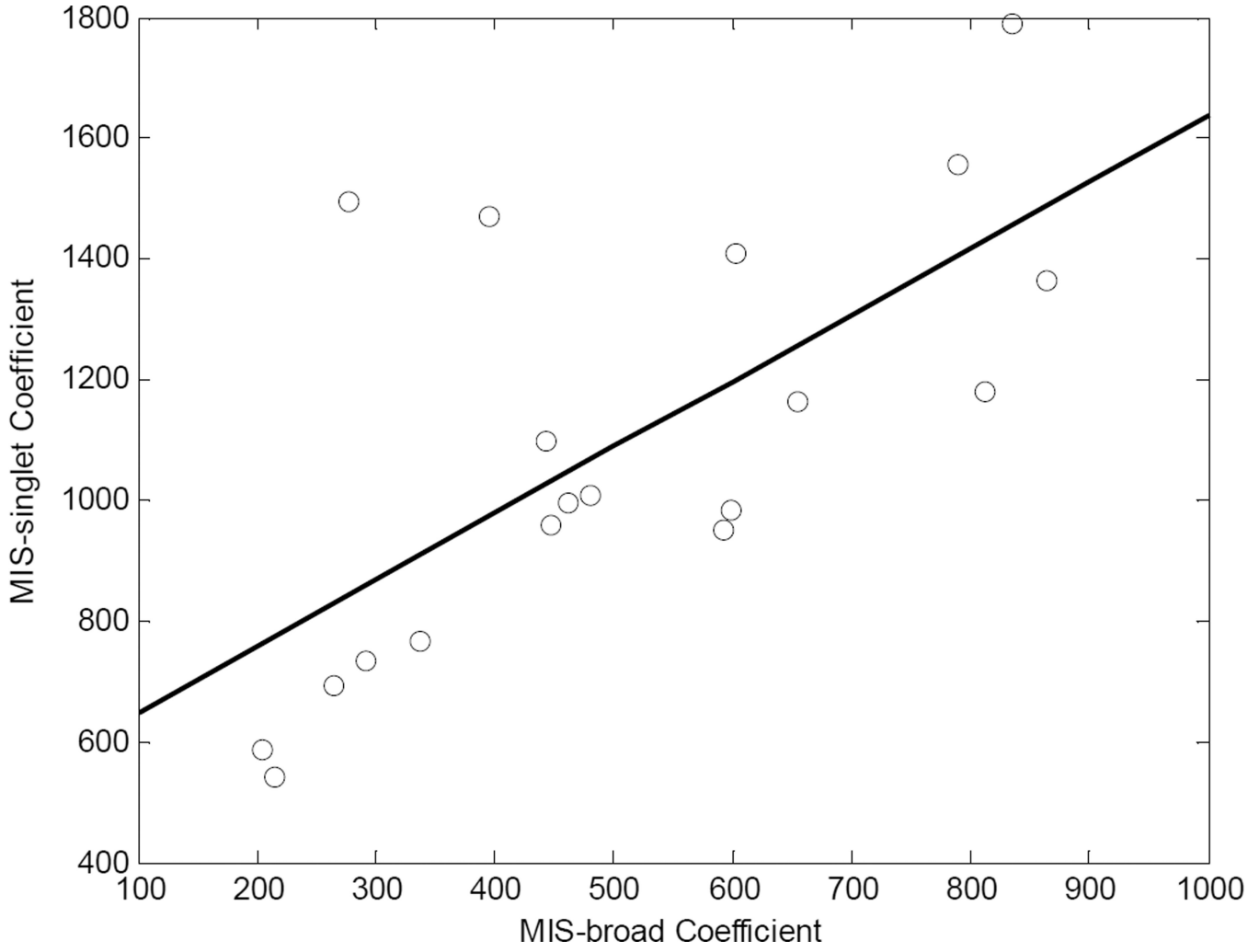

Fig. 8.

Plot of the $MIS_{singlet}/MIS_{broad}$ ratios obtained in the first test of our spectral decomposition method in the analysis of ex vivo irradiated nail clippings. Analysis of the data resulted in a correlation (Pearson) coefficient of 0.68.

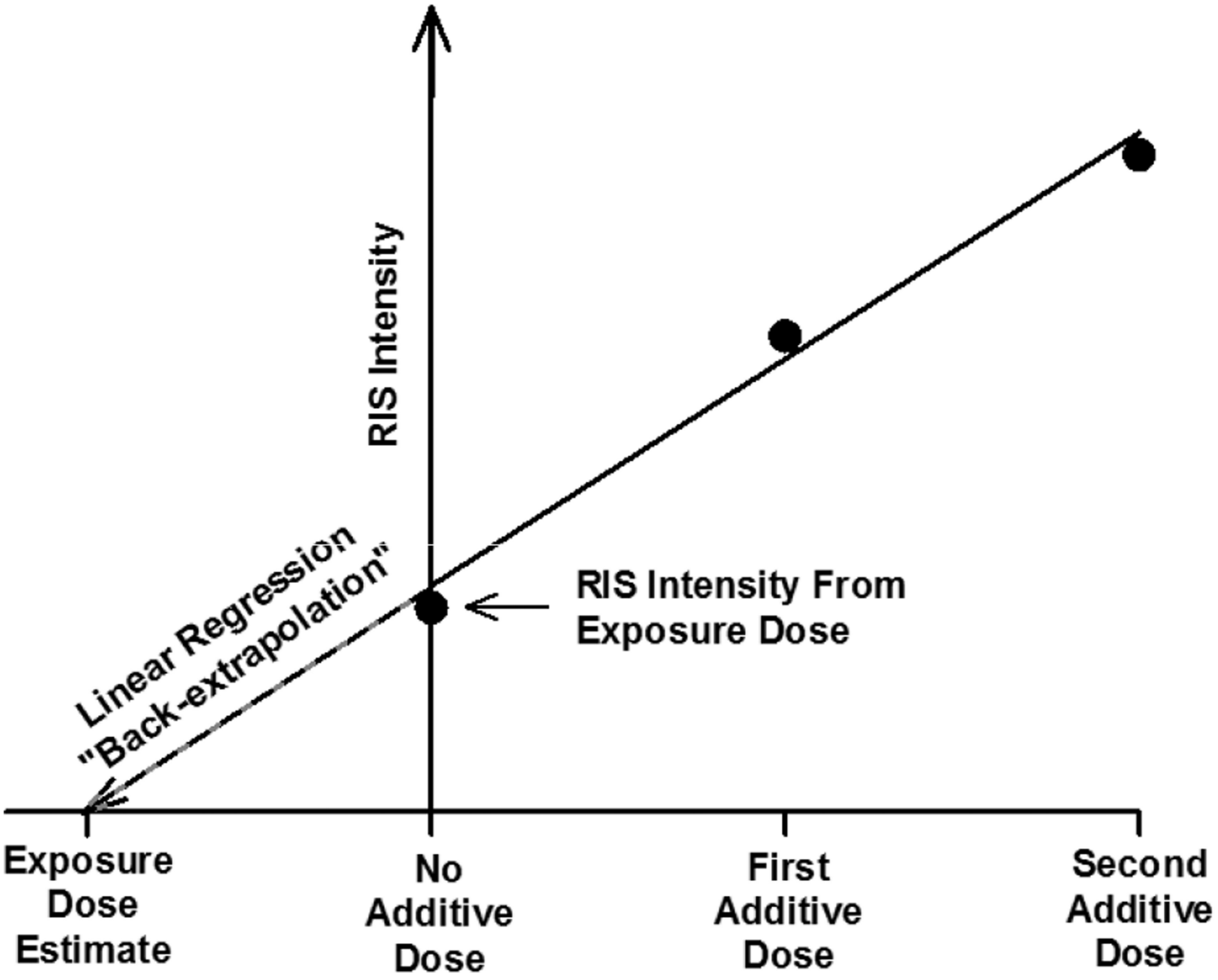

Fig. 9.

Diagrammatic representation of the dose-additive method for calibrating the exposure dose in irradiated fingernails or toenails. In practice, a minimum of two additive doses are needed to analyze linear regression and to gauge linearity in the RIS intensity. Increasing the number of added doses increases the precision of the exposure dose estimate but results in increased analysis time for each nail sample.

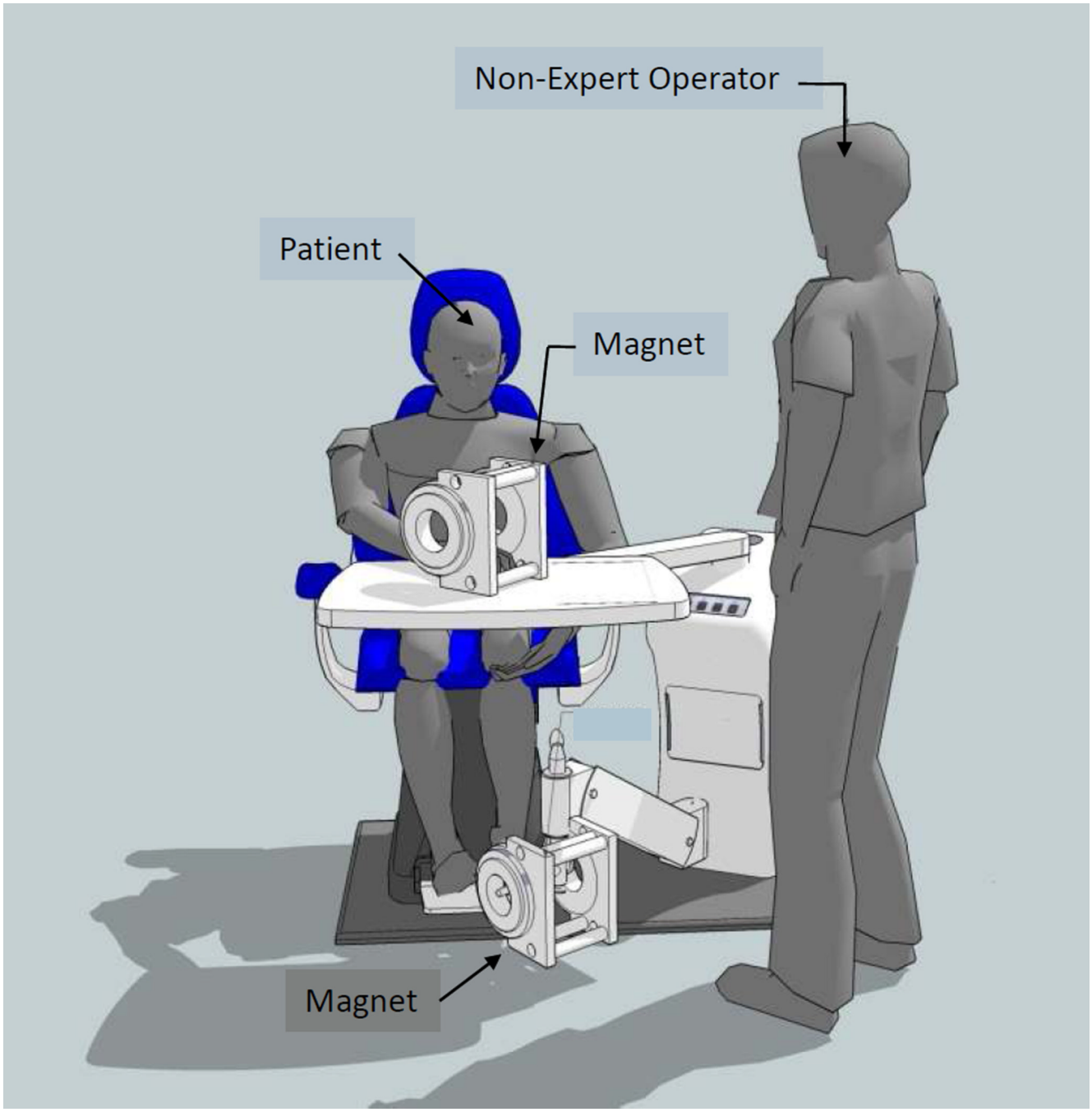

Fig. 10.
Proposed setup for dosimetric measurements of nails on hands and feet.

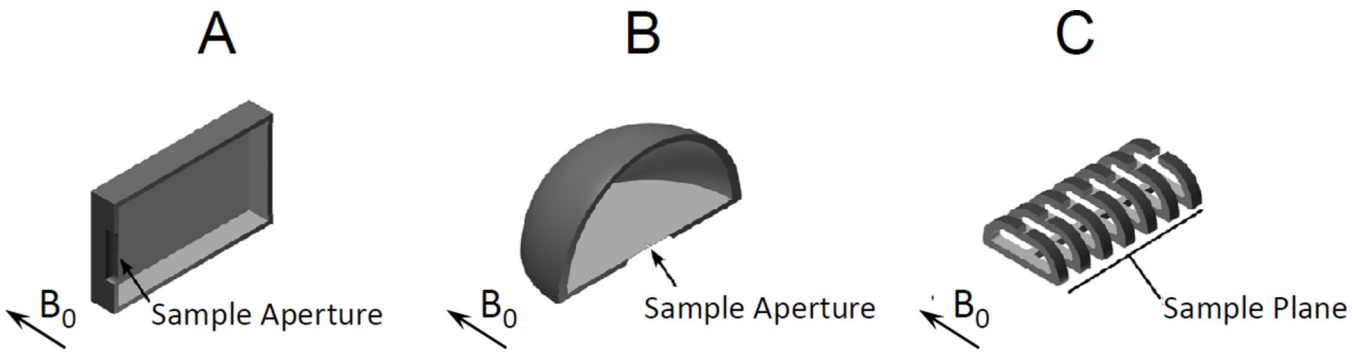

Fig. 11.
The three types of in vivo EPR surface resonators under development: (A) a rectangular TE_{102} cavity aperture resonator; (B) a hemispherical TE_{121} aperture resonator; and (C) a surface resonator array (SRA) with 5×10 mm sampling area.

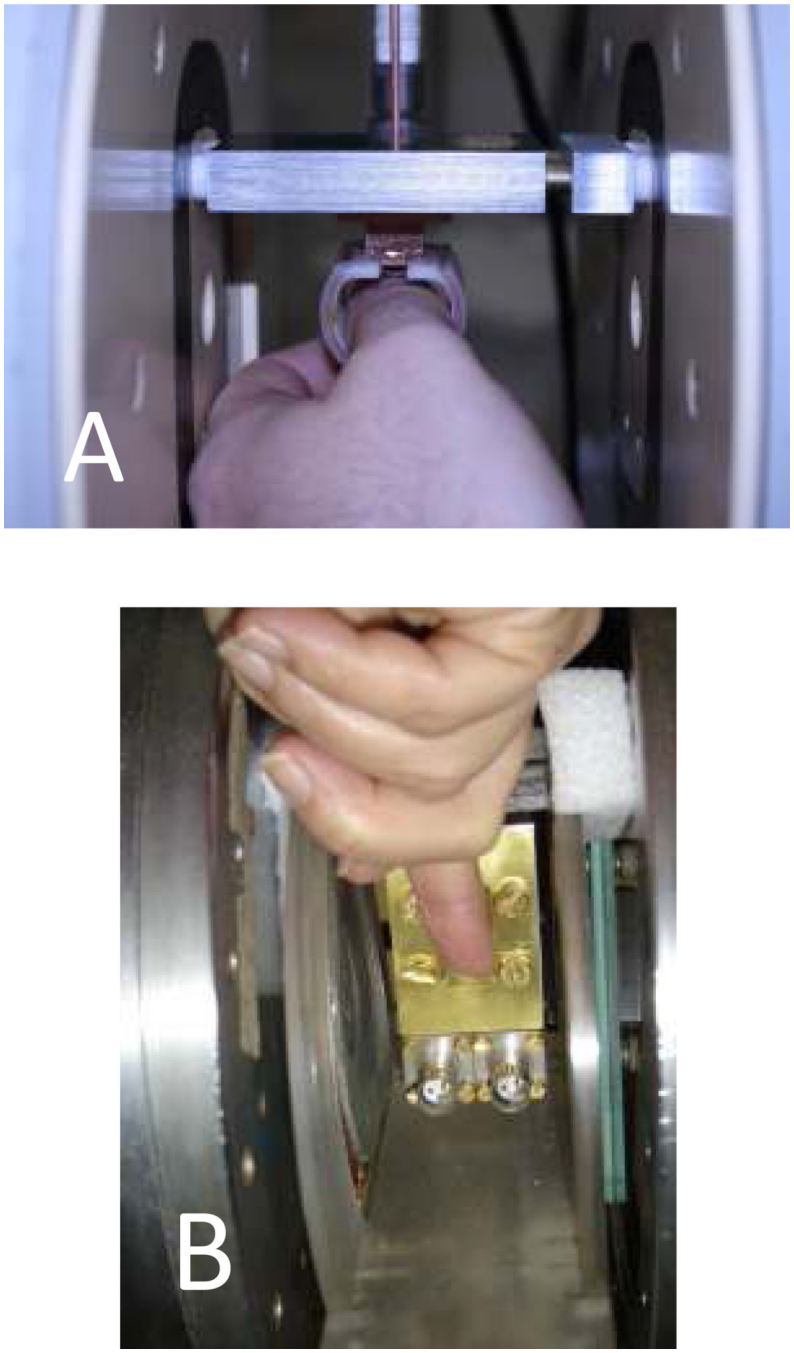

Fig. 12.
Photographs illustrating the position of fingers in (A) the SRA resonator and (B) the aperture resonator.

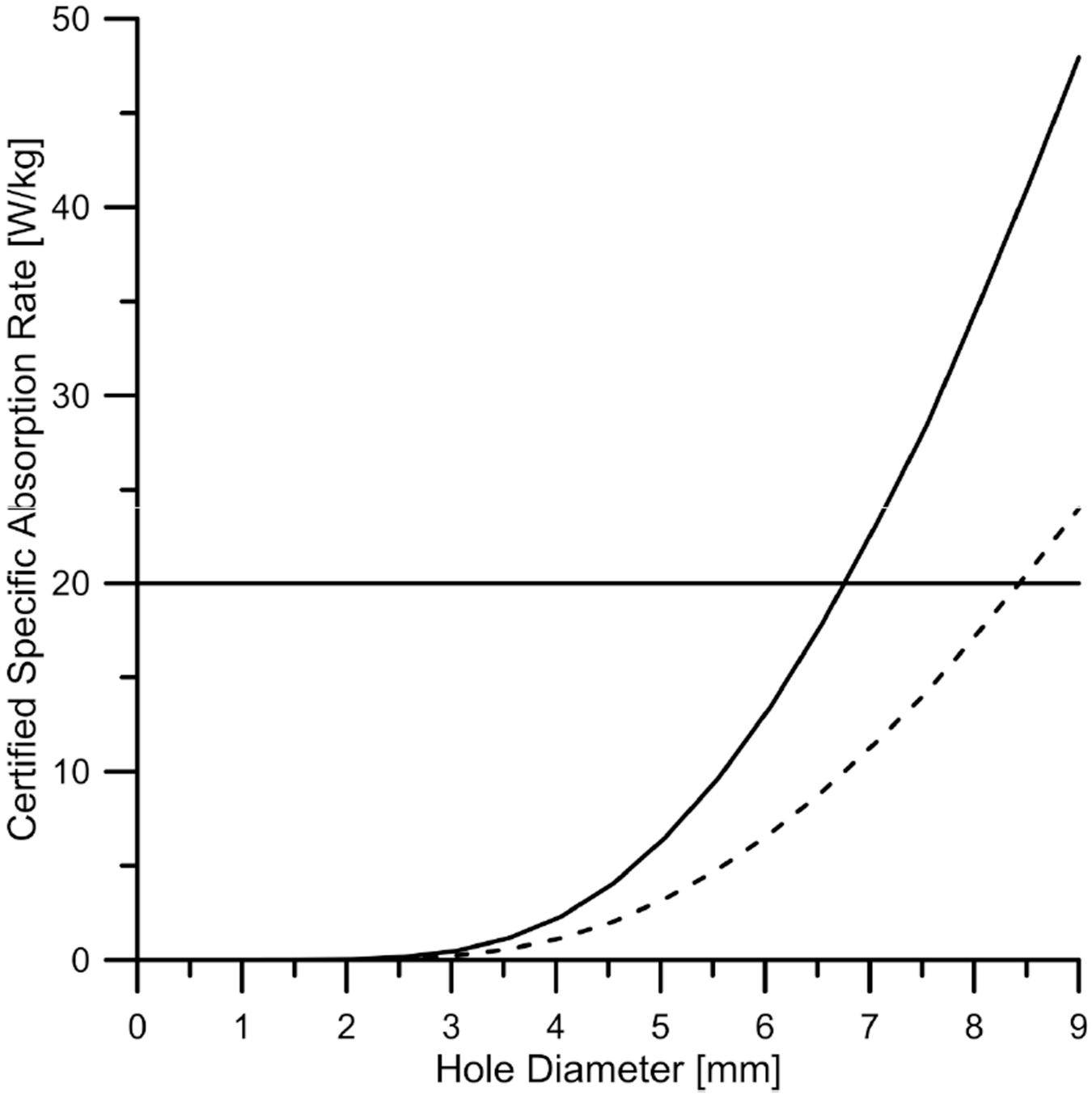

Fig. 13.
Calculated, certified, specific-absorption rate for both the rectangular TE_{102} resonator (dashed) and the hemispherical TE_{121} resonator (solid). All three resonators are compared at the 20 W kg^{-1} SAR specification outlined in IEEE Specification Standard 95.3C-2002 (IEEE 2002).

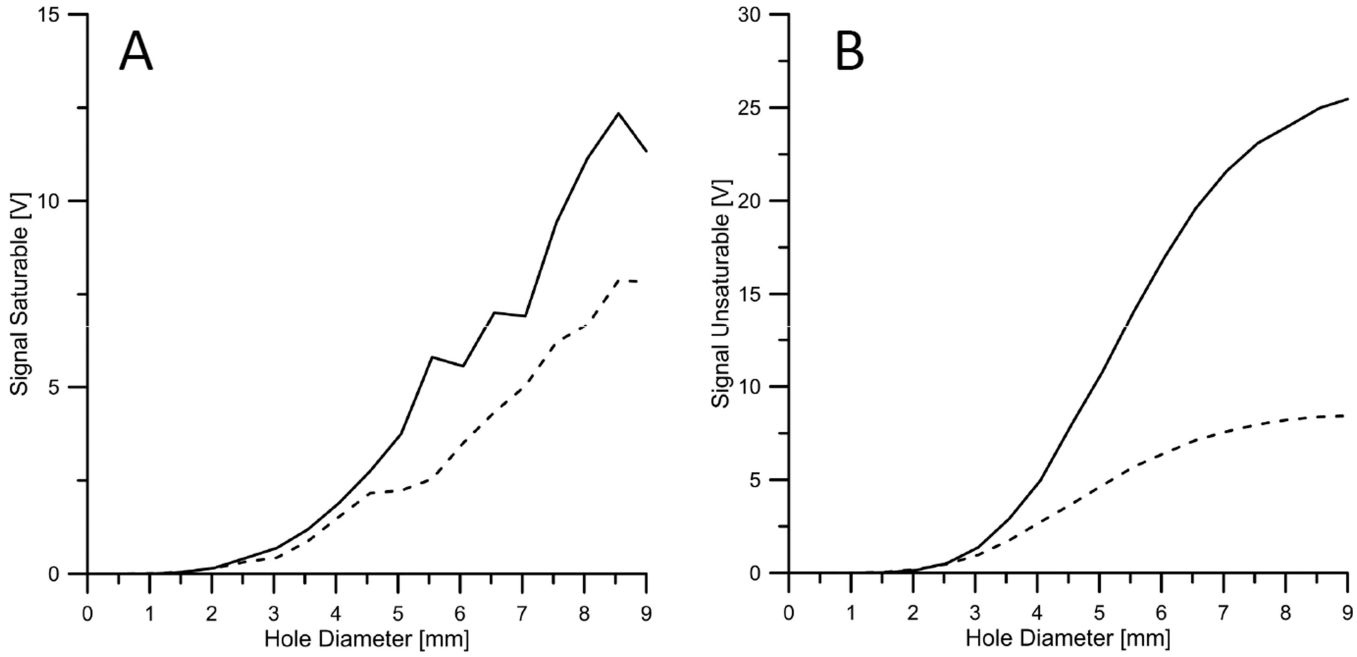

Fig. 14.
Calculated EPR signal intensity versus the aperture size of the hemispherical TE_{121} resonator (solid line) and the rectangular TE_{102} resonator (dashed line). Fig. 14a shows the saturable signal (constant H_1), whereas Fig. 14b shows the unsaturable signal (constant applied power).

Table 1

Characteristics of simulated EPR surface resonators using Ansoft HFSS

Name	TE_{102}	Hemisphere TE_{121}	Surface Resonator Array
Signal Saturable [V]	7.87	5.89	5.716
Signal Unsaturable [V]	8.38	17.01	21.36
Efficiency [G $W^{-1/2}$]	1.167	2.42	3.72
Sample cross-section (mm)	8.55	6.55	5 × 10