EVOLUTION AND OPTIMIZATION OF TOOTH MODELS FOR TESTING *IN VIVO* EPR TOOTH DOSIMETRY

Kyo Kobayashi¹, Ruhong Dong¹, Roberto Javier Nicolalde², Benjamin B. Williams^{1,3}, Gaixin Du¹, Harold M. Swartz^{1,3} and Ann Barry Flood^{1,*}

¹EPR Center for the Study of Viable Systems, Radiology Department, Geisel School of Medicine at Dartmouth, HB 7785, Williamson Translational Research Bldg. Lebanon, NH, USA

²Nicolalde R&D, LLC, West Lebanon, NH, USA

³Division of Radiation Oncology, Department of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

*Corresponding author: Ann.B.Flood@Dartmouth.edu

Testing and verification are an integral part of any cycle to design, manufacture and improve a novel device intended for use in humans. In the case of testing Dartmouth's electron paramagnetic resonance (EPR) *in vivo* tooth dosimetry device, *in vitro* studies are needed throughout its development to test its performance, i.e. to verify its current capability for assessing dose in individuals potentially exposed to ionizing radiation. Since the EPR device uses the enamel of human teeth to assess dose, models that include human teeth have been an integral mechanism to carry out *in vitro* studies during development and testing its ability to meet performance standards for its ultimate intended *in vivo* use. As the instrument improves over time, new demands for *in vitro* studies change as well. This paper describes the tooth models used to perform *in vitro* studies and their evolution to meet the changing demands for testing *in vivo* EPR tooth dosimetry.

INTRODUCTION

In a series of companion papers in this issue, the team from the Electron Paramagnetic Resonance (EPR) Center for the Study of Viable Systems at Dartmouth (the EPR Center) has described several advanced technical developments and clinical tests that have been conducted to evaluate Dartmouth's device for performing EPR *In Vivo* Tooth Dosimetry^(1–4).

Designing and developing any device for use in clinical care requires complex cycles to identify and solve many technical, ergonomic and regulatory problems^(5–7). In addition to these more generic complexities, the design and testing of dosimetry devices, such as those at the EPR Center that are intended for use in a large-scale terrorist event involving radiation, present additional challenges^(8–11). Examples of the additional and special challenges for biodosimetry include: being able to meet the technical requirements to correctly assess dose of large numbers of people within the timeframe needed as well as being able to be operated by people without expertise and with virtually no training and under conditions of a severely compromised infrastructure (such as loss of usual power, water, food, transport and communication networks).

This paper focuses on one aspect of the design cycle that the EPR Center team has had to solve, i.e. the design and development of simple but effective ways to test the device both in regard to its technical performance but also in its readiness to be operational in these especially challenging conditions.

Both because there is no good animal model for human teeth and because the EPR device itself has been designated as a minimal risk device, we have used human teeth in all of our testing. For many evaluations, our tests have used measurements made directly *in vivo* in humans. (This and many other arguments can be readily adapted to apply to the EPR Center's dosimetry devices based on finger and toenails; however, because the focus on this paper is on tooth dosimetry, we do not discuss nail dosimetry here.) For example, ~700 people had been measured *in vivo* using EPR tooth dosimetry by the end of 2015; many of these people had multiple measurements, and some were measured over a several year period.

Nonetheless, for a variety of tests, ranging from detailed time-intensive engineering tests of the sensitivity of resonator prototypes to studies requiring the serial addition of known doses of ionizing radiation to teeth, we needed to also conduct *in vitro* tests using human teeth.

Engineering design cycles

Many have described the engineering design/quality control improvement cycle for a device^(5–7). A common theme describes such cycles as having four stages: planning the prototype, then building it, testing it and finally modifying the design to improve it further. This cycle is then repeated, starting with the new information gathered to improve the design,

with the result that each completed cycle steadily improves the prototype.

The focus of this paper is on one step in this cycle for EPR *in vivo* tooth dosimetry: the step to test the device. While not usually highlighted in the literature on design cycles, the testing step itself often entails a need for the testing models to themselves evolve. This was the case for the *in vitro* tooth models. That is, in a sort of ‘side design cycle’ to the main design cycle to iteratively evaluate the EPR instrument, we also needed to plan, build, test and improve the tooth models themselves and confirm that they were performing well as *in vitro* testing models.

The tooth models: designing *in vitro* tests

Briefly, the simplest ‘tooth model’ used one tooth. Its primary uses have been to test the sensitivity of the EPR resonator, to assess instrumental calibration curves over time and across instruments, to test the software’s performance, to test automation features (such as automated placement of the resonator on the tooth), and to examine variation in background signals associated with normal variation in tooth condition [such as exposure to heavy stains, tooth whitening, medical X-rays, ultraviolet (UV) light, etc.]. These tests have been performed on multiple iterations of the EPR tooth dosimetry device and its principal components, e.g. the resonator or bridge. See Schreiber *et al.*⁽²⁾ and Petryakov *et al.*⁽³⁾ in this issue for an example of related engineering developments and their testing.

Although it is the ‘simplest’ model, these tests required that we develop a structure like the jaw to hold the tooth rigidly in place during measurements and at a physical location within the device that would simulate normal tooth placement during an *in vivo* measurement.

Additionally, the tooth holding structure needed to use materials that did not incidentally interfere with the EPR spectra for assessing dose. They also needed to be easy to use and tolerant of being measured hundreds of times with a variety of resonators. Finally, in order to be useful for tests needing serial irradiation, it was also important to have a tooth model that allowed removal and replacement of the tooth into its holder.

Other tests required more sophisticated *in vitro* models including: (1) anatomically correct full mouth models, e.g. to examine the impact of lossy material in the context of a normal mouth on resonator sensitivity, (2) dentures that would allow placement of an irradiated extracted tooth into a natural gap in a person’s dentition, e.g. to conduct *in vivo* measurements using an irradiated tooth in a unirradiated volunteer and (3) simplified four-incisor models, e.g. to simulate the many natural variations in

the anatomy of the mouth and incisors such as wide gaps, overlapping teeth or excessively twisted angles.

This paper describes the development and evolution of these tooth models to assess the upper central incisors and the materials used. (Not detailed here, the earliest *in vivo* tooth dosimetry instruments measured the molar teeth, which involved prior iterations of tooth models including inserting an irradiated tooth into a natural gap in a volunteer’s dentition.) We first describe the result of the tests to confirm that the tooth models performed as intended. We then briefly summarize the major *in vitro* tests that used the various tooth models developed.

METHODS

Materials and instruments

The materials used in constructing and testing the tooth models include:

- *Putty* (vinyl polysiloxane impression material) (Exaflex[®] Putty)
- *Epoxyes tested as a ‘jaw’ structure in the tooth models* were all variants from the same manufacturer (Double/Bubble[®] Epoxy)
- *Epoxy used as a glue* (Fixmaster[®] Fast Cure Poxy Pak[™] Epoxy)
- *Human teeth* (whole upper incisors without evidence of prior radiation therapy involving the head and with $\geq 90\%$ of the labial surface without caries or fillings, donated at death and provided deidentified and with minimal demographic and health information by the National Disease Research Interchange or Science Care, Inc.)
- *Plastic wrap* (GLAD Press’n Seal[®])
- *Lossy material* (gelatin, ethylene glycol salt and water)
- *Control standard* (White Delrin[®] Acetal Resin).

Details of the EPR *in vivo* tooth dosimetry device have been reported elsewhere^(1–3, 8–14). The tooth being queried by the device reported here was one or both of central incisors in the maxillary jaw. In addition, all *in vitro* and *in vivo* data acquisition and analyses followed the EPR Center’s standard operating procedures (SOP)⁽¹⁴⁾; the only difference between the *in vivo* and *in vitro* SOPs was the need, with *in vivo* measurements, for operators to follow hygienic practices and interact with human volunteers.

The instruments referenced in this paper include:

- *The L-band EPR In Vivo Tooth Dosimetry device* being developed by the EPR Center at Dartmouth
- *X-band EPR* (Bruker EMX-micro EPR instrument)

- *Network analyzer* (Hewlett-Packard 8753A Network Analyzer).

Statistical tests for significance

Dunnett's test was used for multiple comparisons. Student's *t*-test was used to compare two samples. Multiple regression was used to test the impact of age and gender on background EPR signals. A $p \leq 0.05$ was considered to be statistically significant on small samples; $p \leq 0.001$ was used for samples >50 .

RESULTS

Intermediary tests: do the tooth models perform as desired?

Ensuring that materials used to make the model do not impact EPR spectra

Prior to constructing each new design of a tooth model, we tested the materials to be used to ensure that the materials that are in the sensitive volume of the resonator do not have EPR signals that would interfere with the measurements of the teeth. We used the epoxy to build the maxillary structure for the four-tooth model (see Figure 1) and evaluated its EPR signals. The four-tooth model has been used in several important clinical tests of the sensitivity of the current device prototype, as reported in Flood *et al.*⁽¹⁾ and Schreiber *et al.*⁽²⁾ in this issue.

Preparatory to developing this model, we performed a materials test on four candidate epoxies to potentially use to simulate the structure of the maxillary jaw to hold teeth in this model. The epoxies were first molded into a suitable block, using the

Figure 1. A four-tooth model, resting on an acrylic holding-plate that fastens into a stationary platform that holds the model stably and in correct alignment within the magnetic field during measurements. The tooth model platform, also made of non-EPR-sensitive material, serves the same functions as the *in vivo* platform used to rest a person's upper teeth during measurements.

holder for the one-tooth model, so that they could be measured in a materials test using our L-band EPR for *in vivo* teeth dosimetry with our then standard method of five resonator repositionings. We also measured a control standard made of white acetal resin (technically called polyoxymethylene), which is among the strongest and stiffest of thermoplastics commonly used in injection molding applications; this resin had already been tested for other uses involving our device and had been shown to not have a significant EPR signal.

As illustrated in Figure 2, two types of epoxy had an EPR amplitude in the region for assessing dose that was quantitatively close to EPR spectra expected for teeth with an added dose of ~ 5 Gy and was statistically significantly higher than the control ($p \leq 0.05$); these candidate epoxies were discarded for use in the four-tooth model. Of the two remaining potentially acceptable epoxy candidates, Epoxy-D had a high viscosity, which made it more difficult to handle during fabrication (i.e. it dried too slowly) and so Epoxy-C was selected to fabricate the structure of the tooth models with teeth embedded into a stable 'jaw'.

Simulating and testing the quality factor

Another potentially very important characteristic to determine for *in vitro* measurements using tooth models is whether and under what circumstances the tooth models need to simulate the dielectric properties associated with the lossy tissues of the mouth, as characterized by the quality (Q) factor of the coupled resonator. The Q factor is important to take into account in assessing dose because (other things being equal) the amplitude of the EPR signal varies in proportion to the Q factor.

Although not detailed here, studies to develop lossy materials for the tooth models began with

Figure 2. Material testing of four candidate types of epoxy to simulate the jaw for tooth models. The data show the mean and standard deviation of the EPR amplitude (in units of volts) for a measurement made with five resonator repositionings.

using the network analyzer to determine the average Q factor when measuring an upper incisor in the mouth. The average *in vivo* Q was assessed using eight volunteers, each measured with the network analyzer with three resonator repositionings. Other than using the network analyzer instead of the EPR bridge, measurements for Q factor followed the SOP for measuring dose *in vivo*, including the use of the resonator and the standard ‘bite block’ (a platform developed for people to rest their incisors on during measurements). The average Q for these volunteers was 140.

Other tests performed on the simulated lossy materials included re-measurements with the network analyzer over several months, to assess the stability of the lossy materials and to determine the temperature and conditions for long-term storage to avoid any deterioration. A temperature warmer than usual refrigerator temperature was chosen so as to decrease the time needed to bring it to room temperature before measuring the tooth model. In developing these lossy materials, we followed the same procedures and materials (basically gelatin, ethylene glycol salt and water, wrapped in a protective plastic wrap) as others who have simulated the dielectric properties of tissues for testing microwave responses^(15–17).

Figure 3a shows a four-tooth model with three pieces of lossy material representing the lossy tissues of the mouth (named by their location as the lip, chin and tongue). Figure 3b provides evidence that Q varies depending on the lossy material (results compared *in vivo* averages vs tests A–L that varied the number of lossy pieces used, the shape and the water content). These tests were conducted to ascertain how much the water content or size of the lossy material affects the Q and what conditions were easiest to handle and reproduce. Briefly (holding other variables constant), less water content in the tongue piece gave a slightly higher Q (A vs B, C vs D, E vs F, G vs H, I vs J and K vs L) but the lower (40%) concentration was easier to handle. Regarding the lip piece, the Q increased slightly with each trimming of the lossy material. Similarly, the Q increased with the halving or removal of the chin piece. Overall, the findings to note are that we can achieve a desired Q level using lossy material and can simulate well the Q seen in *in vivo* mouth measurements.

While not detailed here, we also conducted a series of tests using serial *in vivo* measurements in patients receiving total body irradiation for treatment of cancers in preparation for a bone marrow transplant and *in vitro* tests using tooth models with and without lossy materials and with varying added doses. These tests confirmed that we could use the simpler tooth models without adding the ‘chin’, ‘tongue’ and ‘lips’ and could reliably convert from *in vitro* to *in vivo* measurements based on calibration curves developed on irradiated patients.

Figure 3. Tooth models simulating *in vivo* lossiness. (a) A four-tooth model encased with three pieces of lossy material, referred to by their location as lip, chin and tongue. (b) Means and standard deviation of Q measurements ($n = 3$ for each variant) made by varying the size and water content of the lossy pieces added to the four-tooth model. Legend A = default model shown in (a). Water content of the tongue was 40% in A, C, E, G, I and K and 70% in B, D, F, H, J and L. The lip was serially reduced in three stages: (1) the initial reduction was to the front, used in C, D, E and F; (2) the front was further reduced in G, H, I and J and (3) also trimmed on the side in K and L. The chin was reduced in half for I, J, K and L and not used in E and F.

Protecting *in vitro* teeth for high use

While performing our tests using the single tooth model, we found that extracted teeth are fairly fragile when measured repeatedly (up to hundreds of times). To protect and reinforce the tooth's labial surface, we started with a glue that we determined had no intrinsic EPR signal. We then tested to ensure that this glue when applied to teeth did not affect the radiation-induced EPR spectra in teeth.

Figure 4 illustrates the use of the protective glue on two incisors that had been irradiated to 5 Gy and that had severe cracks on the labial surface. We provided supportive repair to the surface of each tooth using a SOP (Figure 4a and b). We then measured the EPR signal amplitude immediately before and

Legend: arrows = cracks on surface; NS = not significant

Figure 4. Protecting teeth for high use. (a,b) Two incisors that had developed cracks. The right side of the figure displays the mean and standard deviation of six 60-second EPR measurements, done before and 24 hours after applying protective glue to the cracks.

24 hours after applying the protective glue for both teeth and found no difference (Figure 4a and b) ($p < 0.05$). Continued heavy use of teeth after supportive repair was successful, i.e. there was less or no cracking.

Principal results: testing the EPR instrument's performance using tooth models as *in vitro* tests

For the principal evaluations of the performance of the *In Vivo* EPR Tooth Dosimetry system using *in vitro* models, see the companion papers (especially Flood *et al.*) in this issue. Here, we present three additional examples of using *in vitro* tests to evaluate the performance of *In Vivo* EPR Tooth Dosimetry.

The one-tooth model: does dose assessment need to take into account variation in background signals?

One important performance evaluation of our instrument's ability to accurately assess whether victims of a major radiation event received a dose above the threshold for treatment for Acute Radiation Syndrome rests on our ability to distinguish between the added dose

from an event and the normal background signals in teeth.

As in any analytical measurement, there will always be a background signal and normal variation. Using a clinical example (depending somewhat on the laboratory), normal red blood cell (RBC) counts can range for males from 4.6 to 6.2 mil/ μ l and for females from 4.2 to 5.2 mil/ μ l. The clinician, in determining whether and how to act based on an individual's RBC, needs to consider the general expected range. Likewise for any quantitative estimate of dose to be used for triage, it is important to understand what is the usual expected background or 'normal' value and range and potentially take into account other factors (such as gender in the above example) that might influence the interpretation of the basic data. Therefore, we sought to determine what is the usual background, i.e. 'baseline' EPR signal in our measurements and what if any are factors that might systematically influence the estimated baseline measurement.

Fattibene and Callens⁽¹⁸⁾ have reviewed the literature on the EPR background signal observed in tooth enamel. They conclude that it is composed of both a native signal associated with the enamel,

independently of exposure to ionizing radiation and a radiation-induced component due to medical or environmental/lifestyle exposures to ionizing radiation. Environmental radiation exposures include high energy UV radiation and reflect geographic variations in levels of exposure that influence an individual's cumulative dose depending on where the person has lived or worked.

Because tooth enamel accumulates effects from ionizing exposures over a lifetime, age can be reasonably hypothesized to be predictive of differences in background signals. Similarly, since gender may be related to differences in lifestyle or medical exposures over a lifetime, gender may also predict differences in background measurements. Both age and gender are also readily determined from victims in a major radiation event and so these factors could potentially be built into our analytic methods to adjust the accuracy of our dose estimates.

To explore these types of questions, we used the one-tooth models to amass a database of 'background' measurements (collecting measurements on each tooth at the time it was delivered to the EPR Center). We illustrate one such study below.

Do age and gender predict differences in background EPR measurements?

Because of donor characteristics for the pool of teeth available for this analysis (e.g. virtually all donors were white), we restricted the analysis of the impact of age and gender on our background measurements to white donors who did not have a medical history of radiation therapy. We asked our dentist-experts to examine each tooth and confirm the tooth was an upper central incisor and did not have major fillings on the labial surface. We then restricted this analysis to teeth whose baseline measurements were performed on the current version of the loop resonator described in Flood *et al.*⁽¹⁾. This resulted in 78 measurements, on separate teeth from 47 different donors [47% were female with an average age of 57 y (same for both sexes) and an age range from 17 to 88]. Table 1 presents the results of regressing age and sex and their interaction on the background EPR signal of enamel converted to Gy. In this analysis, the overall regression model was statistically significant ($p < 0.0001$ with $R^2 = 40\%$) but

only the coefficient for age was statistically significant (as expected, the background signal increased with the age of the donor).

These results underscore the importance of considering factors that might be related to variation in background signal and the desirability of utilizing variables that can be easily assessed in the expected conditions where EPR *in vivo* tooth dosimetry will be used (like the age of the person being measured).

Is the dose estimate based on measuring one tooth impacted by the presence of neighboring teeth?

Because there is a large variation in the size of lateral incisors, which are generally much smaller than central incisors and because people may have gaps between teeth and/or capped or missing neighboring teeth, we tested whether and to what extent our estimates based on one tooth were in fact influenced by the proximity of neighboring teeth. To test this concern, we constructed a three-tooth model in which we could insert and extract neighboring teeth (Figure 5). We began this test using a fairly extreme version of 'neighboring teeth' (both were central incisors approximately equal in size to the middle tooth), and all three teeth were irradiated to an added dose of 10 Gy. The middle incisor was measured three times, first with and then without any neighboring teeth. As shown in Figure 5c, there was no significant change in the estimate regardless of having large neighboring teeth suggesting that our estimates may not need to adjust for the presence or size of neighboring teeth.

Other types of testing of the performance of in vivo tooth dosimetry

There were many other studies that have been conducted with the help of *in vitro* tooth models. For example, an important test of performance of our device was the development of automated features and simplified workflow and tasks so that the measurements could be done by a novice operator.

In order to train novices on our procedures for measuring *in vivo*, we developed several four-tooth models. These models ranged from being relatively easy (e.g. large teeth that were ideally aligned in the

Table 1. Regression of age and gender on EPR amplitude of 78 unirradiated upper central incisors from 47 donors.

Independent predictors of EPR baseline	Coefficient	Standard error	p value
Intercept	-0.1420	0.3317	0.670
Age	0.0255	0.0056	≤ 0.0001
Sex (female)	0.0165	0.4615	0.972
Age $\times$ sex interaction	0.0024	0.0077	0.754

Overall model: $R^2 = 40.2\%$, $p \leq 0.0001$; intercept is the expected mean value of y when all predictors are zero.

Figure 5. Three-tooth model with removable neighboring teeth. (a,b) Neighboring teeth in place and removed. (c) Mean and standard deviation of three measurements of the middle incisor measured with and without neighboring teeth. All three teeth were irradiated to 10 Gy. NS, not significant.

jaw) to difficult situations (e.g. buck teeth, retruded teeth, overlapping teeth, tiny teeth, teeth with extra large neighboring teeth, central incisors with a large gap) and used these as ‘training’ for novice operators. A later iteration of these models allowed us to interchange the central incisors (the challenging targets of our measurement) into one ‘jaw’ with permanently mounted lateral incisors, thus reducing the number of lateral incisors we needed to use.

The four-tooth model became a standard for testing the performance of our device in major simulations of *in vivo* testing. When technical performance was the primary goal of testing, we chose incisor teeth from the same donor in order to control for age, gender and any personal exposure history from medical or environmental doses. (In contrast, when the goal of the models was to train new operators, we used incisors from several donors, each of whom had only provided us with one incisor.) The four-tooth model allowed us to also compare measurements of both central incisors from the same donor. This model also facilitated making measurements under conditions where the teeth are held in the natural anatomical

conditions of the jaw and, where appropriate, we could add lossy materials known to simulate *in vivo* Q conditions.

Nonetheless, although the results are not reported here, we have also used these one-tooth models to conduct a series of experiments to examine other potential factors that might influence the background measurements (bleach, stain, ultraviolet, amount of enamel in the tooth, the size and presence of neighboring teeth, etc.).

As a final example of advanced tooth models, we also developed a special version of a one-tooth model that could be used in volunteers with a natural gap with a missing central incisor (such volunteers usually had a temporary or permanent removable denture). For these volunteers, each one-tooth denture model was customized to fit into the person’s gap in dentition and remain stable during measurements. This allowed us to measure several extracted teeth that had been irradiated to different known added doses, both while seated in a person’s mouth and *in vitro*. This provided critical data to validate the use of results obtained *in vitro* to inform measurements

in vivo. It also allowed us to make numerous comparable measurements over time.

CONCLUSIONS

In order to successfully test the performance of the *In Vivo* EPR Tooth Dosimetry device during its advanced development phases, we needed to supplement *in vivo* testing with *in vitro* tests involving human teeth. The resulting tooth models varied in number of teeth, stability and functionality of the holding structures and capability of simulating other dielectric properties (principally based on soft tissues surrounding the teeth measured *in vivo*). All offered the advantages of being able to be measured repeatedly, being measured before and after serial irradiation and not requiring special hygienic or other considerations that *in vivo* measurements entail.

The tooth models have been used in a variety of tests and studies of the EPR device as it evolved and advanced in its development over time. Companion papers present details of their use in engineering developments^(2, 3) and in rigorous tests of meeting performance standards⁽¹⁾. Here we illustrate their use to gather evidence that could improve our estimates by taking into account factors that influence variation in background signals and neighboring teeth.

In addition to the instrumental performance as measured by sensitivity of dose estimates, tooth models have been used to test ergonomic developments and to train new operators as well as to evaluate performance of novice operators, an important goal for the device's intended use for point of care triage in a disaster.

Incidental to its use as an *in vitro* test for EPR but equally important, the tooth models themselves needed to adapt and evolve to be useful. With each evolution and change in the tooth model, tests of the model's performance also needed to be performed. These model tests are also briefly described here, including materials testing to ensure the materials used to construct or hold the tooth models would not interfere with EPR dose estimation. The necessity of and capability for simulating lossiness of the mouth and the preparation for unusually high use (such as thousands of intense and rapid repositionings of the resonator during many engineering tests) are illustrated in this paper.

In summary, the *in vitro* testing using the tooth models has been an integral and successful component of the overall strategy to design an effective *in vivo* device for tooth dosimetry.

ACKNOWLEDGEMENTS

We gratefully acknowledge the advice and technical help of others at the EPR Center (Holly Boyle,

Eugene Demidenko, Matthew Feldman, Shireen Geimer, Ankit Gupta, Maciej Kmiec, Jean P. Lariviere, Sergey V. Petryakov, Tim Raynolds, Kevin Rychert, Wilson Schreiber, Dimitriy Tipikin and Victoria Wood) and consultants: Paul Calderon and Masaichi-Chang-Il Lee.

DISCLOSURES

H.M.S. and A.B.F. are owners of Clin-EPR, LLC, a small company that manufactures EPR spectrometers for *in vivo* investigational use.

FUNDING

This research was supported by the National Institute of Allergy and Infectious Diseases of the US DHSS' National Institutes of Health (NIH) under Award Number U19-AI091173 and contract HHSO100201100024C with the Biomedical Advanced Research and Development Authority (BARDA), within the Office of the Assistant Secretary for Preparedness and Response, US Department of Health and Human Services.

REFERENCES

1. Flood, A. B., Williams, B. B., Schreiber, W., Du, G., Wood, V. A., Kmiec, M. K., Petryakov, S. V., Demidenko, E., Swartz, H. M., and the EPR Center Tooth Dosimetry Project Team. *Advances in in vivo EPR tooth biodosimetry: meeting the targets for initial triage following a large-scale radiation event*. Radiat. Prot. Dosim. (forthcoming in same issue) doi:10.1093/rpd/ncw165.
2. Schreiber, W., Petryakov, S., Kmiec, M. M., Feldman, M. A., Meaney, P. M., Wood, V. A., Boyle, H. K., Flood, A. B., Williams, B. B. and Swartz, H. M. *Flexible, wireless, inductively coupled surface coil resonator for EPR tooth dosimetry*. Radiat. Prot. Dosim. (forthcoming in same issue) doi:10.1093/rpd/ncw153.
3. Petryakov, S., Schreiber, W., Kmiec, M. M., Williams, B. B. and Swartz, H. M. *Surface dielectric resonators for X-band EPR spectroscopy*. Radiat. Prot. Dosim. (forthcoming in same issue) doi: 10.1093/rpd/ncw167.
4. Williams, B. B., Flood, A. B., Demidenko, E. and Swartz, H. M. *ROC analysis for evaluation of radiation biodosimetry technologies*. Radiat. Prot. Dosim. (forthcoming in same issue) doi:10.1093/rpd/ncw168.
5. Deming, W. E. *The New Economics for Industry, Government, and Education* (Boston, MA: MIT Press) (1993). ISBN 0262541165.
6. Nelson, E. C., Batalden, P. B., Godfrey, M. M. and Lazar, J. S. *Value by Design: Developing Clinical Microsystems to Achieve Organizational Excellence* (San Francisco, CA: Jossey-Bass) (2011).
7. Pahl, G., Beitz, W., Feldhusen, J. and Grote, K.-H. *Engineering Design: A Systematic Approach*, third ed. (London, UK: Springer-Verlag) (2007). ISBN 1-84628-318-3.
8. Swartz, H. M., Williams, B. B., Flood, A. B., Meineke, V. and Dorr, H. *Comparison of the needs for biodosimetry*

- for large-scale radiation events for military versus civilian populations. *Health Phys.* **106**, 755–763 (2014). doi:10.1097/HP.0000000000000069.
9. Flood, A. B., Ali, A. N., Boyle, H. K., Du, G., Satinsky, V. A., Swartz, S. G., Williams, B. B., Demidenko, E., Schreiber, W. and Swartz, H. M. *Special needs of the military for radiation dosimetry for tactical warfare against deployed troops: comparing military and civilian needs for biodosimetry methods.* *Health Phys.* **111**(2), 169–182 (2016). doi:10.1097/HP.0000000000000538.
 10. Swartz, H. M., Iwasaki, A., Walczak, T., Demidenko, E., Salikov, I., Lesniewski, P., Starewicz, P., Schauer, D. and Romanyukha, A. *Measurements of clinically significant doses of ionizing radiation using non-invasive in vivo EPR spectroscopy of teeth in situ.* *Appl. Radiat. Isot.* **62**, 293–299 (2005).
 11. Swartz, H. M. *et al.* *Electron paramagnetic resonance dosimetry for a large-scale radiation incident.* *Health Phys.* **103**(3), 255–267 (2012). doi:10.1097/HP.0b013e3182588d92.
 12. Williams, B. B., Sucheta, A., Dong, R., Sakata, Y., Iwasaki, A., Burke, G., Grinberg, O., Lesniewski, P., Kmiec, M. and Swartz, H. M. *Experimental procedures for sensitive and reproducible in situ EPR tooth dosimetry.* *Radiat. Measure* **42**, 1094–1098 (2007).
 13. Williams, B. B., Dong, R., Kmiec, M., Burke, G., Demidenko, E., Gladstone, D., Nicolalde, R. J., Sucheta, A., Lesniewski, P. and Swartz, H. M. *Development of in vivo tooth EPR for individual radiation dose estimation and screening.* *Health Phys.* **98**, 327 (2010).
 14. Williams, B. B., Flood, A. B., Salikhov, I., Kobayashi, K., Dong, R., Rychert, K., Du, G., Schreiber, W. and Swartz, H. M. *In vivo EPR tooth dosimetry for triage after a radiation event involving large populations.* *Radiat. Environ. Biophys.* **53**, 335–346 (2014). doi:10.1007/s00411-014-0534-9.
 15. Robinson, M. P., Richardson, M. J., Green, J. L. and Preece, A. W. *New materials for dielectric simulation of tissues.* *Phys. Med. Biol.* **36**, 1565 (1991).
 16. Ibrahim, W. M. A., Algabroun, H. and Almaqtari, M. T. *Short Review on the Used Recipes to Simulate the Bio-Tissue at Microwave Frequencies* (Berlin Heidelberg: Springer) (2008). ISBN 978-3-540-69138-9.
 17. Lazebnik, M., Madsen, E. L., Frank, G. R. and Hagness, S. C. *Tissue-mimicking phantom materials for narrowband and ultrawideband microwave applications.* *Phys. Med. Biol.* **50**, 4245 (2005).
 18. Fattibene, P. and Callens, F. *EPR dosimetry with tooth enamel: a review.* *Appl. Radiat. Isot.* **68**, 2033–2116 (2010). doi:10.1016/j.apradiso.2010.05.016.