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LONG-TERM BIODOSIMETRY REDUX

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This paper revisits and reiterates the needs, purposes and requirements of biodosimetric assays for long-term dose and health risk assessments. While the most crucial need for biodosimetric assays is to guide medical response for radiation accidents, the value of such techniques for improving our understanding of radiation health risk by supporting epidemiological (long-term health risk) studies is significant. As new cohorts of exposed persons are identified and new health risk studies are undertaken with the hopes that studying the exposed will result in a deeper understanding of radiation risk, the value of reliable dose reconstruction is underscored. The ultimate application of biodosimetry in long-term health risk studies would be to completely replace model-based dose reconstruction—a complex suite of methods for retrospectively estimating dose that is commonly fraught with large uncertainties due to the absence of important exposure-related information, as well as imperfect models. While biodosimetry could potentially supplant model-based doses, there are numerous limitations of presently available techniques that constrain their widespread application in health risk research, including limited ability to assess doses received far in the past, high cost, great inter-individual variability, invasiveness, higher than preferred detection limits and the inability to assess internal dose (for the most part). These limitations prevent the extensive application of biodosimetry to large cohorts and should be considered a challenge to researchers to develop new and more flexible techniques that meet the demands of long-term health risk research. Events in recent years, e.g. the Fukushima reactor accident and the increased threat of nuclear terrorism, underscore that any event that results in significant radiation exposures of a group of people will also produce a much larger population, exposed at lower levels, but that likewise needs (or demands) an exposure assessment. Hence, the needs for retrospective dose estimation are likely to be greater in the future. The value of biodosimetry can be considerably enhanced with the development of new or improved methods, particularly with suitability for application at long periods of time after exposure.

INTRODUCTION

This paper revisits and reiterates the needs, purposes and requirements of biodosimetric assays for a long-term assessment of dose and health risk research as previously discussed by Simon *et al.*[1, 2] There are at least two important reasons to revisit these issues now. First, since the last publication[2] that discussed such needs, Japan and the world experienced the Fukushima nuclear reactor disaster. That event resulted in exposures to clean-up workers as well as large public thyroid cancer screening programmes[3, 4]. Moreover, the event triggered worldwide interest and concern about the possible radiation exposures received and the reliability of projections of excess cancers based on the estimates of exposure. The Fukushima event underscored that unexpected and unpredictable events leading to mass exposures that require radiation dose estimation may take place at any time and without warning. A second reason for revisiting the concepts of biodosimetry and long-term assessments is the ever increasing threat of terrorist activities and the likelihood that radioactive material will be used in a dirty bomb or fission device that could expose groups of people ranging from a few tens to thousands or more. Both reasons support the argument that there is a vital need to develop additional and/or improved biodosimetric assays that can serve any of the three purposes: (i) to support medical decision making for high dose exposures in accidents and for medical triage for large groups of persons potentially exposed to a radiation accident or terrorist event, (ii) to provide confirmation of low doses to 'worried well' populations or those for whom medical intervention may not be necessary and (iii) to support health risk analyses of exposed populations by reducing uncertainty in retrospective dose estimation. Future radiation accidents or terrorist events involving radiation will likely require retrospective exposure assessment for larger-sized groups than for small industrial accidents and those needs may continue for years, particularly if long-term health risk research is not begun until years after the exposure takes place. While cohorts for study are ideally chosen because necessary information for dose reconstruction is available, in many cases, such information is found to be completely lacking for some persons and highly uncertain for others.

The need for dose assessments soon after exposure (i.e. within a few days) appear to be well recognised[5] and numerous programmes and significant funding are focused on development of assays and mitigation agents. The needs of exposure assessments at long periods of time after exposure[1] (6 months

to many decades), however, are, in our view, less than fully recognised or appreciated. Because it sometimes takes years to identify and trace a cohort as well as design and implement an epidemiological study[6], and because there is often a many-year latency time before radiation-related cancer appears, health risk research often begins after significant time (6 months to many years) following the exposure event.

It is our thesis that any event that results in radiation exposures (whether alleged or true makes little difference) with an immediate need for dose assessment to a group will, in most cases, result in a subsequent long-term need for the assessment for a larger group (usually with lower exposures). Moreover, those needs may continue for many years because of identification of new persons or groups who were exposed or to support long-term radiation health risk studies.

DISCUSSION

Needs and purposes

The general needs and purposes of dose reconstruction are 5-fold[7, 8] and all can potentially be supported or improved by application of biodosimetric assays:

- Management of radiation emergencies, e.g. providing input to decisions on protection of emergency workers and members of the public or medical treatment of exposed or contaminated individuals.
- Confirm success of radiation protection programmes.
- Provide exposed individuals or populations with information on doses they received.
- Determine the likelihood that an individual's disease might have been induced by exposure to radiation (e.g. for compensation or litigation)
- Investigate dose–response relationships in epidemiological studies to improve understanding of radiation risk.

Improving our understanding of radiation risk is particularly important since the first four objectives above implicitly assume radiation exposure to be a causal agent of biological damage or cancer risk. Our scientific understanding today that allows quantitative assessment of radiation-related health risks in humans are derived primarily from human epidemiological studies[9–12]. Despite decades of study, numerous questions about radiation risk remain including:

- Extrapolation from high to low dose?
- Acute vs. chronic exposure?
- Internal vs. external exposure?
- Dependence on age at exposure?
- Gender dependence?
- Dependence on ethnicity?
- Sensitive populations?
- Sensitivity of different tissues?
- Stochastic vs. acute effects?

Continued study of exposed populations can potentially resolve many of the above questions, though to produce risk models that can result in dependable and quantitative risk estimations, reliable dose estimation is essential. For that purpose, epidemiological studies must rely on retrospective dose estimation supported by one or more types of data: (i) exposure data derived from properly designed and employed dosimeters (as in occupational studies), (ii) environmental radioactivity measurements and models of the transport of radioactive materials in the environment (for environmental exposure studies) or (iii) measurements from biodosimetric assays of exposed persons.

Limitations of present methods and ideal characteristics for new methods

The requirements of precision in estimated doses for health risk research are generally equal or greater than other purposes. For example, in screening populations medical management who may have been exposed for hours or days earlier from an accident or terrorist-related event, the level of precision in dose estimation needed is relatively crude (e.g. <2, 0–4, >4 Gy)[8, 13]. Such requirements are clearly less than that is needed for epidemiological purposes. Only in the case of small, potentially high dose accidents involving a few persons and where there may be significant inhomogeneity of exposure over the body, is good precision needed to tailor appropriate medical response. In those cases, doses can be provided by dose reconstruction, biodosimetry or a combination of techniques.

Radiation epidemiological studies typically rely on relatively accurate and unbiased estimation of doses to specific organs of individuals, rather than the whole body, in order to derive reliable estimates of risk of cancer or other health outcomes. Typically, estimation of doses <500 mGy to specific organs of individuals is needed.

Despite the potential value of biodosimetry to health risk studies, limitations of presently available methods constrain their widespread application in long-term health risk research. The limitations from the point-of-view of usefulness to long-term health risk studies include: (i) most methods to assess doses are not capable of estimating exposures far in the past, (ii) high costs per sample or high costs for equipment and supplies, (iii) large inter-individual variability, (iv) invasiveness, (v) higher than preferred detection limits and (vi) inability to assess internal dose (for the most part).

As outlined elsewhere[2], there are various characteristics that would make a biodosimetry method ideal from the point of view of assisting long-term health risk studies. These include:

- Register the actual absorbed energy in a single identifiable tissue regardless of type of ionising radiation to which it is exposed;
- Be specific to ionising radiation;
- Have a radiation-induced signal that is stable over long periods of time (tens of years at minimum);
- Have a well-characterised dose–response;
- Have low inter-individual variation;
- Have a low minimum detectable dose (on the order of a few tens of milligray) or at least, be able to measure doses that are as low as those received by a substantial fraction of the subjects of the epidemiological study;
- Have moderately good precision (on the order of $\pm$ 30%) at two times the minimum detectable dose (and possibly better at higher doses);
- Have good accuracy (low bias);
- Be field-friendly;
- Depend on minimally invasive sampling;
- Produce measurements that can be interpreted to reflect doses in other organs besides the tissue assayed; and
- Have low per-sample cost.

In addition to the list above, further desired characteristics would include being able to discern:

- Partial-body from whole-body exposure (with a degree of quantification);
- Variation of doses between organs;
- Acute from chronic irradiation, and
- Doses received from radiations of different quality.

Past use of biodosimetry in epidemiological research and current capabilities

Few summaries of the use of biodosimetry in radiation health risk research are available. See Simon *et al.*[1, 2] for a listing of many studies as well as other publications in this special issue. Large epidemiological studies that have employed biodosimetry include cohorts from the Chernobyl accident, Techa River releases and A-bomb survivors. Those studies have, for the most part, used biodosimetry to measure doses to individuals and used those measurements to corroborate model-based estimates and/or reduce estimation uncertainty.

An important point, however, is that no epidemiological study to our knowledge has been conducted that has relied solely on biodosimetry. Moreover, few studies have relied on it for dose estimation for more than a few percent of the study cohort. The reasons for the relatively low use in any single epidemiological study has generally been the difficulty in obtaining samples (e.g. teeth or blood samples), high cost of assays, high detection limits and low reproducibility of measured values.

As discussed elsewhere[1, 2], only two biodosimetric assays (EPR of tooth enamel and chromosome painting or FISH for stable translocations) are useful at long periods of time after exposure, e.g. years to decades. Both techniques have primarily been used to assess externally delivered dose though either measurements, in principal, reflect (but cannot differentiate) exposure from radioactivity internally deposited in the body.

The practical lower limit of detection for *in vitro* EPR measurements of tooth enamel is a few tens of milligray[14]. The practical limit of detection of dose to bone marrow by the FISH assay[15] increases with age (due to age-related increases in chromosome translocation rates), suggesting detectable doses range from about 70–150 mGy for adults ranging from 30 to 70 years of age. While the limits of detection of these assays are suitable for many health risk studies, the invasiveness and high cost still preclude extensive use.

CONCLUSIONS

In this discussion, we have reviewed that biodosimetry has been shown to be a useful tool for assessing doses to ionising radiation soon after exposure, particularly for those exposures that were unexpected and for which no routine radiation monitoring was in place. In addition, biodosimetry has proved to be useful to augment model-based dose reconstruction in long-term health risk studies, most commonly to corroborate analytical or model-based dose estimates, to assess bias in models and their dose estimates and to reduce uncertainty in individual doses. However, despite the advantages that biodosimetry might bring, it is presently not possible to use it extensively in health risk studies because of numerous practical limitations discussed.

In addition, it is our thesis that any event that results in true or alleged exposures of a group and is accompanied by a related and immediate need for dose assessment will, in most cases, result in the need for a dose assessment, usually to a much larger group of persons with lower exposures. Moreover, those needs may extend over a many-year period particularly if (i) health risk research is not begun until years after the exposure takes place, (ii) necessary input data for dose reconstruction is found to be lacking or highly uncertain, or (iii) new individuals are identified at later times that want or require exposure assessment. Only for the situations when the exposed population is restricted to an occupational accident, e.g. a criticality accident, or an event with a recognised

number of persons, e.g. a medical over-exposure, will there not be a larger public population with true or alleged exposures.

Finally, we note that at present, there are only two proven assays for assessing radiation dose at long periods of time after exposure, those being *in vitro* EPR analysis of tooth enamel and the use of chromosome painting (FISH) in peripheral blood lymphocytes to assess chromosome translocations. Both assays often have difficulty with reproducibility, though even if considered as acceptably reliable, each have significant limitations in terms of invasiveness, cost of assays, minimum detection limits as well as availability.

In our view, there is not only an opportunity, but a true need for the development of additional biodosimetry assays that overcome some of the present limitations of *in vitro* EPR and FISH. Ideally, it would be desired to have a toolbox of techniques from which one or more can be chosen to best address the needs of the exposure event and the subsequent analysis of the related health impact. We reiterate here, as discussed in Simon *et al,*[2] that it is our intention to stimulate research into the development of new and improved biodosimetric methods that can function in ways beyond medical triage following radiation accidents. While is not possible to know what tools might be developed in the future, it might be prudent today to collect as many biological samples from exposed persons as possible and to store them in ways to maintain their integrity. The samples might include, for example, blood or components of genetic material, tooth, nails and bone.

Because an understanding of radiation risk underpins all efforts and programs to control intentional and unintended exposures, researchers should be cognizant of the potential contribution that new biodosimetry assessment tools could make to the science and practice of radiation protection.

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