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NEUTRON DOSIMETRY: THE LONG-TERM IMPACT OF ADVANCES IN RADIOBIOLOGY

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Neutron dosimetry: the long-term impact of advances in radiobiology

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ABSTRACT

Recent developments in the ability to measure nanoscale radiation effects in body tissue, and in the understanding of cell biology, are likely to lead to proposals for new ways of measuring radiation risk. There may be a step change in dosimetry concepts and techniques. This report considers consider how these issues will affect the facilities and services that standards laboratories, including NPL, will need to provide for neutron dosimetry in the long term.

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1 INTRODUCTION

When it first became apparent that exposure to ionising radiation had adverse health effects, efforts were made to quantify the level of risk. Early attempts were based on the ionisation of gases, and subsequently the concept of absorbed dose (radiation energy deposited per unit mass) was introduced.

Absorbed dose works well for the deterministic effects of high doses. However, for the stochastic effects of low doses (cancer induction for example), it was noticed that different types of radiation, or different energies of the same type of radiation, had different health effects for the same absorbed dose.

This problem was addressed by applying empirical weighting factors to absorbed dose, and this is still the approach in use today. However, it is not particularly satisfactory. The empirical factors are based somewhat subjectively on a variety of sources, such as mouse studies (which may differ from the human case in unrecognised ways) and epidemiological studies with large uncertainties. The factors were not derived from direct consideration of cell biology, and future studies might favour different values.

In recent years the understanding of DNA and cell processes has improved significantly, and techniques have been developed to study the interaction of radiation with matter on distance scales of nanometres. This raises the possibility of defining new risk quantities that are much more directly related to observable and measurable processes in cells, and considerable efforts in this direction are currently under way.

If these efforts are successful, it is possible that dose standards may become more biology-related than at present, and the skills and facilities needed in a dose standards laboratory may change. The aim of this report is to assess whether the approach to neutron dosimetry is likely to change significantly over the next ten years or so, and if so what new resources a standards laboratory would need to develop over that time scale.

2 THE PRESENT APPROACH TO DOSIMETRY

2.1 GENERAL CONSIDERATIONS

Two types of dose quantity are in use: protection quantities, defined by the International Commission on Radiation Protection (ICRP)[1], and operational quantities, defined by the International Commission on Radiation Units and Measurements (ICRU)[2]. The former are used to specify dose limits, but are not directly measurable. The latter are intended to provide reasonable estimates of the protection quantities and to serve as calibration quantities for dosemeters.

The protection quantity ‘effective dose’, E, is given by

$$E = \sum_{\mathrm{T}} \sum_{\mathrm{R}} w_{\mathrm{T}} w_{\mathrm{R}} D_{\mathrm{T,R}}$$

where w_{T} and w_{R} are empirical weighting factors covering different tissue types T and radiation types R, and $D_{\mathrm{T,R}}$ is the absorbed dose averaged over the tissue or organ T due to radiation R. The weighting factors w describe all the biology, yet only nine radiation factors and thirteen tissue factors are defined to cover all types and energies of radiation and all tissue types in the body. This illustrates the extent to which biology is currently simplified in radiation protection.

The operational quantity ‘dose equivalent’, H, is defined using a different approach. H is equal to the product QD at a point in tissue, where D is the absorbed dose and Q is the ‘quality factor’. In this case it is Q which encapsulates the biology, and for charged particles it is a simple function of the unrestricted linear energy transfer L of the radiation in water:

$$\begin{aligned} Q(L) &= 1 && L < 10 \text{ keV/µm} \\ &= 0.32\,L - 2.2 && 10 \leq L \leq 100 \text{ keV/µm} \\ &= 300 / L^{1/2} && L > 100 \text{ keV/µm}. \end{aligned}$$

For photons, $Q = 1$, while for neutrons of a particular energy E_n it is derived by first calculating the absorbed dose distribution $D(L, E_n)$ of the heavy charged particles released by the neutrons, and then applying the $Q(L)$ function as defined above:

$$Q_n(E_n) = \frac{1}{D}\int Q(L)D(L, E_n)dL\,.$$

(See, for example, Ref. 3.)

Area survey meters are typically calibrated in terms of 'ambient dose equivalent' $H^*(d)$, which is defined at a point in a radiation field as the dose equivalent that would be produced by the corresponding expanded and aligned field in the ICRU sphere at a depth of d mm on the radius opposing the field direction. Dose meters designed to be worn are typically calibrated in terms of 'personal dose equivalent' $H_p(d)$, which is defined as the dose equivalent in soft tissue at d mm below a specified point on the body. (A 30 × 30 × 15 cm slab phantom is usually an adequate substitute for the human torso, although strictly the applicable quantity in that case is $H_{p,slab}(d)$.) For both ambient and personal dose equivalent d is commonly set to 10.

2.2 NEUTRON DOSE STANDARDS

The aim of a dose standards laboratory is to provide a wide variety of radiation fields in which the quantities used to calibrate dose meters (currently $H^*(10)$ and $H_p(10)$ typically) can be accurately and precisely determined for a given irradiation.

For neutrons, this is not conventionally done by measuring absorbed doses. Instead, the physical quantity measured is the fluence (number of neutrons per unit area), and this is converted directly into the desired dose quantity using internationally-accepted conversion coefficients.

2.2.1 Measurements of neutron fluence

At NPL, neutron fluences from accelerator-based sources are measured using a calibrated long counter[4, 5], which consists of a BF_3 thermal neutron detector embedded in a moderator.

For irradiations with radionuclide sources, the best precision is obtained by characterising each source in terms of its total neutron output (neutrons per second into 4π steradians) using the NPL manganese bath[6, 7], and its anisotropy of emission using a long counter[8]. The fluence rate for a given irradiation can then be calculated from the geometry. Corrections for radioactive decay are made using the known half-life of the nuclide (including, for ^{252}Cf sources, allowance for the presence of ^{250}Cf), and the manganese bath measurement is repeated at intervals.

At other standards laboratories, other techniques may be used.

2.2.2 Fluence to Dose Equivalent conversion coefficients

Recommended values for coefficients that convert from neutron fluence to ambient and personal dose equivalent with $d = 10$ are set out in ICRU Report 57[9]. They are given at 47 energies between 1 meV and 20 MeV, with a recommended algorithm for interpolating between energies, and at 6 angles of incidence where this is applicable.

These values were derived from Monte Carlo calculations carried out by five research groups, mostly in 1993 and 1994 (see Table 6 in Reference 9). All the groups calculated $H^*(10)$ and two calculated $H_{p,slab}(10)$.

It is notable that a practical set of coefficients was produced, and then evaluated and adopted by an international body, in the space of just a few years, despite the significant effort required and the limited computing resources available in the early 90s.

2.3 PROBLEMS WITH THE PRESENT APPROACH

The existing approach is highly empirical, with no explicit reference to the physics of radiation interactions in cells or to the cell biology that determines the subsequent response of the cells. The weighting factors are instead derived from (for example) mouse studies, where the animal model might differ from the human case in unknown ways, and on epidemiological studies where the doses

are typically both uncertain and higher than those applicable to radiation protection. High dose data need to be extrapolated to lower doses, and it is not clear how this should be done; it is usual to assume a linear response with no threshold, but other relationships are also possible, including ones where low doses actually improve radiation tolerance (the so-called hormesis effect[10, 11]).

It would clearly be desirable, particularly from a metrological point of view, to move away from an empirical system to one more soundly based on physical and biological principles and measurements.

3 PROGRESS TOWARDS RADIOBIOLOGY-BASED QUANTITIES

3.1 EUROPEAN PROJECTS RELATING TO RADIOBIOLOGY

Table 1 illustrates the current extent of the international effort to address dosimetry-related issues including the concerns set out above. It lists several large European projects, mostly at least partly EC-funded, that have been or are being undertaken with aims relevant to the above issues.

Table 1 Recent and current European projects relevant to radiobiology-based dosimetry. (Alphabetical listing.)

Name	Dates	Summary of remit (or relevant section thereof)
ANDANTE	2012 – 2015 inclusive	Combine radiation physics, radiobiology, and epidemiology to re-evaluate the relative cancer risk from neutrons *c.f.* that from photons.
BioQuaRT	June 2012 – May 2015	Develop techniques for measuring the physical characteristics of ionising particle tracks, and investigate how these correlate with biological effects.
DoReMi	2010 – 2015 inclusive	Low-dose research towards multidisciplinary integration: promote the sustainable integration of low-dose risk research in Europe. E.g. Task 5.6: Use the physical-biological Monte Carlo code PARTRAC to investigate initial damage formation and its progression.
EURADOS TC-IR	2013 -	Technical Committee on Ionising Radiation (Roadmap 3, novel dosimetry concept). Aims: *inter alia*, establish a traceability chain of biological dosimetry to physical standards of ionising radiation / develop biological standard systems.
ROSIRIS (IRSN)	2009 -	Study the mechanisms giving rise to secondary effects in radiotherapy. Combines radiopathology, radiotherapy and physical dosimetry, and simulates particle interactions using the Monte Carlo toolkit GEANT4 –DNA.

In addition to the entries in the Table are projects such as OPERRA (Open Project for European Radiation Research), MELODI (Multidisciplinary European Low Dose Initiative) and CONCERT, which have been set up to co-ordinate, integrate and (possibly jointly) fund research in this area of work.

3.2 RADIATION PHYSICS: AVAILABLE APPROACHES TO CELL STUDIES

3.2.1 Microdosimetry and Tissue-Equivalent Proportional Counters

Microdosimetry is the study of the spatial and temporal distribution of radiation interactions in μm-scale volumes. It is typically carried out using a tissue-equivalent proportional counter (TEPC). These are made of tissue-equivalent materials and have ordinary macroscopic dimensions, but are operated at such a low gas pressure that they act equivalently to a cell-sized volume of 1 g/cm^3 matter. Particles entering the chamber are typically energetic enough to cross it easily, so the energy deposited is related to the linear energy transfer L of the crossing particle, and hence contains information on radiation quality. This makes the instrument very useful for studying dose equivalent.

3.2.2 Nanodosimetry and track structure studies

In nanodosimetry, ionisation tracks are studied at nm resolutions (the same size scale as a DNA base pair). At this scale, energy deposition can no longer be regarded as a smooth continuous process, and instead the process must be considered in terms of discrete individual ionisations.

The clustering of these ionisations is significant. Single-strand breaks in DNA, caused by ionising radiation, are common and are easily repaired by the cell because the intact strand retains the required base sequence. Breaks affecting both strands are much harder to repair correctly, and if the cell survives it may do so with an erroneous and possibly carcinogenic version of the genome. Such double breaks are of course more likely when the ionisations are densely clustered.

The number of ionisations caused by a particular track in a specific volume is known as the ionisation cluster size, and nanodosimetric studies typically measure the probability distribution of cluster sizes. As with microdosimetry, the size of the target region is made manageable by using low density material. For example, the track structure rig Startrack[12,13] uses a sensitive region approx. 4 mm on a side together with a gas pressure of 3 mbar to simulate regions of approx. 20 nm dimensions in tissue. The rig is used in conjunction with a tightly-focused (< 1 mm) low-intensity ion beam.

3.2.3 Microbeams and the Bystander Effect

A microbeam facility is one in which an accelerator beam is engineered to be focusable to micrometre dimensions, to allow a precisely known number of particles to be delivered to a particular cell, or part of a cell (e.g. the nucleus), in a living culture. The PTB microbeam facility[14], for example, can produce a beam size of approx. 2 µm outside the vacuum system, with a target accuracy of 2 µm, and automatically deliver single protons or alpha particles to individual cells.

X-ray and electron microbeams also exist, and the Radiological Research Accelerator Facility (RARAF) at Columbia University, NY, has even successfully developed a neutron microbeam[15]. This unusual facility uses the kinematics of the ^{7}Li(p,n) reaction just above threshold to produce exclusively forward-directed neutrons. A neutron spot less than 20 µm in diameter is calculated to be possible, and approx. 30 µm (smaller than a human fibroblast cell) has already been achieved[16].

Microbeams are used to study the response of cells to low doses of radiation, particularly the ‘bystander effect’. This is the occurrence of a biological effect in cells that have not themselves been irradiated but are merely a close neighbour of a cell that has. The effect is understood to be due to chemical signals from the irradiated cell, and is another illustration of the complexity of radiation interactions in cells.

3.2.4 Multiscale and biological studies

Palmans *et al.*[17] make the case very clearly that all the approaches described above, from micrometre to nanometre scales, will have to be combined in order to capture all relevant processes. The computational simulation of interactions at this range of scales is very challenging, and while the available codes (MCNP6, Geant-DNA and many others) are being continuously improved, there is still a great deal to do in terms of including all the necessary interaction processes and cross sections for all the relevant materials.

Furthermore, the bystander effect points to damage mechanisms that are currently only poorly understood. It is certainly clear that direct DNA strand breaking is not the only mechanism that needs to be studied. Other cell structures (for example the mitochondria or the cell wall) can be affected, and it is also possible for radicals and reactive species created by the ionisation event to cause DNA or other damage by chemical reaction. This may happen in the immediate vicinity of the initial event or after diffusion to a location some distance away. Epidemiological studies of atom bomb survivors (see, for example, Reference 18) indicate that non-cancer effects, e.g. cardiovascular problems, also occur. One way to investigate the complex biochemistry that governs cell physiology is to measure changes in protein expression[19].

4 DISCUSSION

The interaction of radiation with cells is an extremely complex process. The initial event may trigger a cascade of processes that eventually leads to pathology, and the initial target may be quite a different cell component from the one that finally fails.

Nevertheless there is a strong will within the radiation protection community to formulate new biologically-relevant dosimetry quantities, as demonstrated by the number of projects under way with this aim in their remit. The present risk quantities seem uncomfortably empirical, and a sounder theoretical basis is highly desirable. Such a sound understanding might also answer currently controversial issues such as whether there is a dose threshold below which radiation poses no risk. It might also be possible to adjust dose limits to take account of the variation in radiation sensitivity from one individual to another.

In the light of this strong commitment it is very likely that biologically-based quantities will be set up and mandated for use, although this may take more than the 10-year timescale that this report considers.

At present, radiation risk quantities are defined in terms of absorbed dose, multiplied by weighting factors or a quality factor. For therapy-level dosimetry of the main non-neutron radiation types (photons, electrons and protons), primary standards are accordingly commonly based directly on measurements of deposited energy, via graphite or water calorimeters[20]. In day-to-day neutron metrology at radiation protection levels, however, the quantity measured is actually fluence (neutrons per cm^2), which is much more straightforward to determine than absorbed dose. Use of the more convenient quantity has been made possible by a one-off exercise in calculating the dose equivalent due to a given fluence, carried out by a few groups in the early 1990s using Monte Carlo codes (see section 2.2.2).

It is likely that the new biological risk quantities will, like the present ones, be defined in terms of dose because that is the approach with which non-neutron practitioners are familiar. There is also a great deal of expertise in radiation calorimetry within the standards community. From a neutron metrologist's point of view, it will be highly desirable to establish the relationship between these new quantities and the neutron fluence, so that the latter quantity can continue to be used. The existing conversion coefficients were calculated and standardised relatively quickly, and this gives cause for optimism that the same will be possible for the new ones.

Determining and agreeing the new coefficients may be more difficult than was the case for the old, given that a much more complex calculation may be called for, and that measurements with a track structure rig or a microbeam may be required if they are part of the definition and are too complex to be simulated satisfactorily. In that event a substantial effort from National Measurement Institutes may be required, and each would have to decide how comprehensively it wished to participate. One way or another, however, new conversion coefficients are likely to emerge, allowing the conduct of neutron metrology to continue in much the same way as before.

In the unlikely event that the new quantities are for some reason not amenable to calculation, an extensive change to neutron metrology, with new experimental facilities and an unaccustomed emphasis on biology, is likely to be necessary. However, such a change would probably be signalled some years in advance as the new quantities are proposed and discussed. Neutron metrologists need to participate actively in the discussions now under way, to make sure that the neutron perspective is given due consideration and to provide early warning if problematic changes appear likely. Practitioners working with other radiation types may in fact come to appreciate the fluence approach used in neutron work, leading to a greater unity of the different branches of radiation protection.

The central role of Monte Carlo simulation in the derivation of the existing conversion coefficients, and its likely equally important role for the new ones, highlights the importance of nuclear data in radiation protection.

5 SUMMARY AND CONCLUSIONS

- Despite the formidable obstacles, new biology-based quantities for radiation protection are likely to emerge eventually, although not necessarily within the next decade.
- It is probable that a one-off exercise (which may require substantial effort) will provide conversion coefficients between the new quantities and neutron fluence, in which case no fundamental changes to the practice of neutron metrology will ultimately be required.
- Neutron metrologists need to participate in the discussions on biology-based quantities, to make sure that the neutron perspective is clearly presented, and to provide early warning to the neutron community of any proposals that are not well-suited to neutron work.
- The likely central role of Monte Carlo simulation in the derivation of the fluence conversion coefficients highlights the need to establish and maintain comprehensive libraries of nuclear data.

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