RBE and radiation weighting factors as applied in the context of protection of the environment from ionising radiation

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Abstract
It has long been recognized that the degree of biological impact on an organism resulting from a given absorbed dose of ionising radiation can vary depending upon the type of radiation involved. This difference has been experimentally quantified and reported as the "relative biological effectiveness" (RBE) of specific radiation types. RBE values have been measured for a variety of end points in *in vitro* experiments that include human and animal cell lines, as well as *in vivo* experiments with animals. Such studies have shown that the magnitude of a biological effect depends not only on dose and the type and energy of the radiation delivering the dose, but also on the rate at which the dose is delivered and, most importantly, the endpoint under study. The need to apply this knowledge to radiation protection of humans has led to an aggregation and analysis of RBE data to develop such constructs as "radiation weighting factors". In recent years, radiation protection has taken on a broader meaning, and is now evolving to include protection of the environment from ionising radiation. However, the application of radiation weighting factors in the context of assessing biologically significant doses to animals and plants is not without some controversy. Protection of biota from the effects of ionising radiation has largely focused on endpoints which are relevant at the population level, such as reduced reproductive fitness. This means that use of radiation weighting factors derived from evaluations of stochastic effects, as in the system of protection for humans, appears inappropriate. This presentation discusses efforts to develop a logical, transparent, and defensible approach to establishing radiation weighting factors for use in assessing impacts to non-human biota. It also considers the challenges in differentiating stochastic from deterministic impacts.
Keywords: RBE, Radioprotection, Environment, Reference Animals and Plants,

1. BACKGROUND

The work discussed in this paper represents an overview of an on-going critical evaluation of radiation effects data undertaken for ICRP Committee 5, Protection of the Environment. The purpose of this task group was to review the scientific literature on RBE as it relates to both stochastic and deterministic effects. Studies on "exotic particles", such as heavy ions, or particles with very high (GeV) energies were excluded unless their LET was similar to alpha or beta radiations. Ultimately the review included data on alpha particles, fission neutrons, and tritium. The goal of the task group was to recommend a dose-modifying value suitable for application in the protection of non-human biota, including both deterministic and stochastic effects in the review. The information presented here is subject to revision as new data is included. The final report of the Task Group is also subject to review and comment by the Main Commission of the ICRP as well as organizations external to the ICRP.

This presentation relies to a great extent on previous reports by the ICRP and other organizations or investigators. Most of those reports were prepared to support the development of recommendations on biological effectiveness for purposes of radiological protection of humans. Nonetheless, given that much of the available data was obtained from studies of radiation effects in biological systems other than those of human origin, much of the previous work is directly relevant to protection of the environment.

2. RBE AND RADIATION WEIGHTING FACTORS

Studies of dose-response relationships for different types of radiation in inducing a wide variety of effects in many biological systems, ranging from cells in culture to whole organisms, have shown that knowledge of the absorbed dose is not sufficient to characterize the biological response from a given dose. As early as 1931 (Failla and Henshaw) it was recognized that the degree of biological impact varies by radiation type for the same absorbed dose. It has long been recognized that RBE is influenced by dose, dose-rate (or fractionation of dose), the spatial distribution of energy imparted at the microscopic level as well as the density of ionizations created there. Sixty years ago the term "linear energy transfer" (LET) was initially used to describe the loss of energy as a charged particle moved through matter (Zirkle, Marchbank et al. 1952). It is generally observed that LET is important in determining the response from a given absorbed dose. In particular, high-LET radiations (e.g., alpha particles and neutrons) are more effective per unit absorbed dose than low-LET radiations (e.g., orthovoltage X rays and higher-energy photons) in inducing biological responses, including stochastic and deterministic effects. To account for this, the absorbed dose (in Gray) is often multiplied by a modifying factor in order to account for the Relative Biological Effectiveness (RBE). Strictly, the term RBE only applies to observations from experimental studies and are specific to the endpoint and system studied, environmental and exposure conditions (e.g. reference radiation, dose rate, and dose) amongst other factors. When applied to environmental dose calculations for non-human biota, judgemental dose modifying factors (based on experimental RBE data), have often been referred to as (biota) radiation weighting factors, although a specific terminology has not yet been formally adopted.

RBE is a unitless quantity that is calculated for a specific radiation (A) of interest. It is the ratio of the dose of a reference radiation required to produce a specific level of response to the dose of radiation (A) producing an equal response. All variables, except radiation quality, are held as constant as possible (e.g., see ICRP, 1990). It is a calculated radiobiological quantity that does not require the dose-response relationships have the same functional form (e.g., a linear-quadratic or linear) relationship for the radiations being investigated.

Comparison of RBE values is complicated by the use of varying reference radiations. Examples include [226]Ra gamma rays, (Chen 2004), X-rays (e.g., 200 and 250 kVp) and other photon sources including ^{137}Cs and [60]Co. The net result is that there can be significant differences in the biological effect from the same absorbed dose of these reference radiations. This becomes problematic when developing a radiation weighting factor from RBE values developed from multiple reference radiations.

Effects considered in the calculation of RBE include cancer induction, cell killing, and life shortening, just to name a few (ICRP 1990, 2003, Barendsen 1968). Impacts that directly affect reproduction and the sustainability of populations are considered paramount (ICRP 2008) in regards to developing radiation weighting factors in the context of protection of the environment.

Estimates of RBE generally depend on the nature of the biological endpoint under study—i.e., whether the effect is stochastic, or deterministic. Deterministic effects include impairment of tissue integrity and function, but also include cellular responses. Cellular reproductive death is presumed to be the most significant source of deterministic effects (ICRP 1984). Deterministic effects are presumed to have a threshold, and occur because sufficient damage has occurred such that underlying repair is not possible. The severity of the effect therefore increases with added dose.

Stochastic radiation effects are characterized by the lack of a threshold. Conceptually, this means that a single event (i.e., radiation damage to one cell) is sufficient to cause the effect. In humans, examples of stochastic effects of radiation exposure include cancer and hereditary effects. The frequency of the effect is related to the dose, but not its severity. Radiation weighting factors derived from the radiobiological study of stochastic effects are traditionally used in human radioprotection. However, radiation effects at the chromosome and cellular levels usually do not translate into detriment at the population level and hence, the RBE for stochastic effects in an individual member of the species is of limited concern for population level effects in non-human biota. Traditionally, radiation protection of biota has largely

focused on limiting population relevant deterministic effects, such as reduced reproductive fitness arising for example from effects on fertility, fecundity, growth and survival.

2.1. Factors Influencing RBE

Although most biological effects can be classified as either stochastic or deterministic, there can be substantial variations in RBEs for either type of effect, depending on the particular effect and the biological system under study. As a consequence, judgement is often required in evaluating whether an RBE for a particular endpoint in a particular biological system is relevant to the principle concern in a system of radiological protection of non-human biota, for example maintaining the viability (reproductive capability) of populations of the most sensitive species in radiological protection of the environment.

Both stochastic and deterministic (non-stochastic) effects are used in the calculation of RBE. The functions used to describe effects have two general forms – linear and linear quadratic (ICRP 2003):

$$E_n(D_n) = \alpha_n D_n \qquad\qquad 1.$$

and

$$E_\gamma(D_\gamma) = \alpha_\gamma D_\gamma + \beta_\gamma D_\gamma^2 \qquad\qquad 2.$$

where E_n exhibits a linear response and is the effect typically observed with high LET radiations (such as neutrons) from an absorbed dose D_n. A linear-quadratic effect, E_γ is generally observed from sparsely ionizing radiation (such as gamma photons) receiving an absorbed dose D_γ. The constant α represents the initial slope of the survival curve in the low dose region. The β term describes the curvature at higher doses.

Electrons, gamma rays and X-rays, which are classified as low LET radiation, exhibit LETs in the range of 3.5 keV/µm or less. However, in radiobiological studies, the difference in the effects among low LET radiations may be considerable (ICRP 1990). In comparison, naturally occurring alpha particles, with their energy range on the order of 4-6 MeV, have a resultant LET of ~100 keV/µm.

Unless there is a linear relationship between dose and effect for both the test and reference radiations the RBE will vary with the level of biological damage that is being assessed. RBE is calculated as a ratio of the reference radiation dose to the dose of the test radiation (ICRP, 2003):

$$R(D_\gamma) = \frac{D_\gamma}{D_n} \qquad\qquad 3.$$

However, the value of RBE varies depending on the level of effect being considered (Fig 1). The ratio $D_{\gamma\,High}/D_{n\,High}$ may be different from $D_{\gamma\,Low}/D_{n\,Low}$. Fig.2 illustrates how RBE caries as a function of LET and endpoint (after ICRP 1990 and Barendsen, 1968).
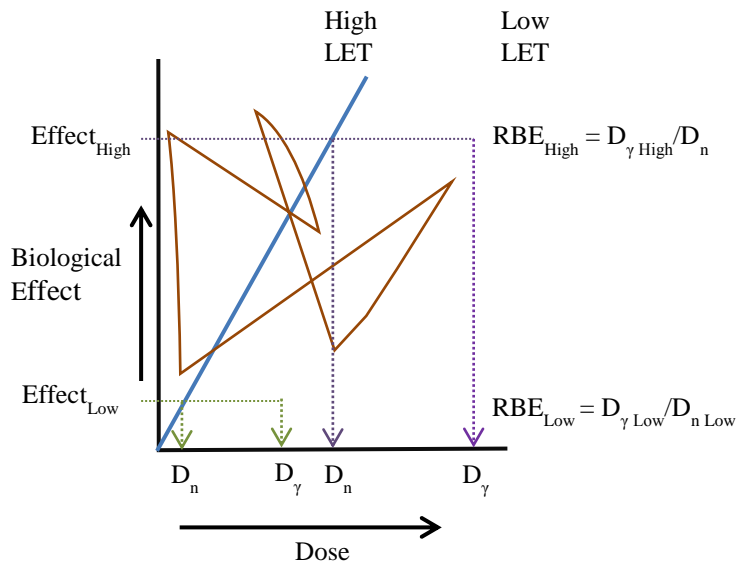
Fig. 1. Example of an RBE calculation for high LET radiation at high and low levels of biological effect.
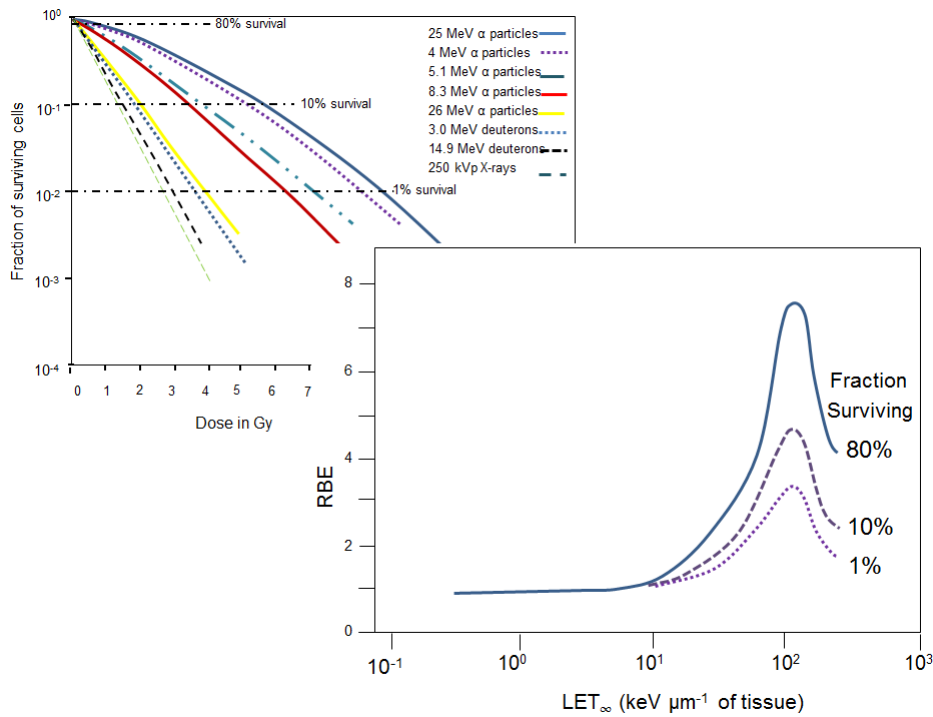

Fig. 2 An example of how dose and LET impact the estimation of RBE (after Barendsen, 1968 and ICRP 1990).

2.2. RBE at minimal doses – RBE$_M$ and RBE$_m$

When RBE is plotted as a function of dose it reaches maximal values as the dose drops below approximately 0.1 Gy of x-rays.   Fig 3. illustrates this effect (after Barendsen 1968). An approximation from the empirical data therefore needs to be made to calculate a maximal value of RBE. The ICRP introduced the term RBE$_M$ to represent the maximal value derived for stochastic effects, e.g., carcinogenesis (ICRP /ICRU, 1963).
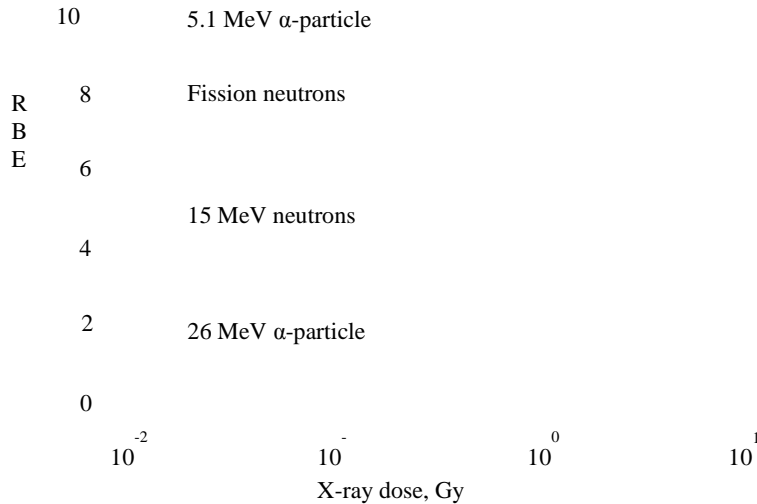
10   5.1 MeV α-particle

R   8   Fission neutrons
B
E   6

       15 MeV neutrons
4

2   26 MeV α-particle

0

10^{-2} 10^{-} 10^{0} 10^{1}

X-ray dose, Gy

Fig. 3. RBE values approach a maximal value, RBE$_m$ at doses ~ 10^{-1} Gy of x-rays; based on survival curves shown in Fig 5, after ICRP 58 (1990) and Barendson (1968).

A similar response for deterministic endpoints also exists, and the term RBE$_m$ is used to designate the estimated maximal value of RBE.   This may seem somewhat curious, as deterministic effects are presumed to have a threshold, in which case an RBE at doses below a threshold would be indefinite. However, estimation of RBE$_m$ was judged to be "necessary for assessing the risk of exposure conditions where a small dose of high-LET radiation is delivered together with low-LET radiation" (ICRP, 1990). From Fig. 3 it can be observed that an extrapolated RBE for deterministic effects is largely independent of dose below ~ 0.1 Gy, a level that may be comparable to a threshold. This means that an estimate of RBE$_m$ may not differ greatly from an estimate of RBE that would apply at doses where significant deterministic effects might occur. Finally, a review of the literature had previously suggested that maximal RBE values derived for stochastic effects tended to be larger than those found for studies of deterministic responses. RBE$_m$ ranged from 2 to 5 whereas RBE$_M$ ranged from 4 to more than 20 (Barendsen 1992).

One of the challenges presented to this Task Group was the necessity to estimate RBE$_m$ and RBE$_M$ from the published data. There are several approaches that can be considered, with the methodology explained in greater detail by ICRP (1990, 2003). The reader is cautioned that the formulation has changed somewhat between these two publications. The dose-dependence of high-LET radiations no longer includes a quadratic term, so that a function used for estimating RBE$_M$ for acute doses is as follows:

$$RBE_M \left(\frac{1 + D_\gamma}{\frac{\alpha_\gamma}{\beta_\gamma}} \right) \cdot [R(D)]_\gamma) \tag{2.2}$$

where all terms have been previously defined.

3. OVERVIEW OF FINDINGS

Hundreds of candidate studies were identified for review by the Task Group. A process was established whereby the committee removed from further consideration those papers which had not been subject to peer review, or where the dosimetric assessment was not clear, or because the radiation type was not relevant. In some instances it was not possible calculate RBE_m and RBE_M from the available data.

3.1. Overview of findings for alpha emitters

Table 1 summarizes the data included for alpha emitters.   Table 2 tabulates the number of papers, and classifies the endpoints, test models, and RBE values that were reported or calculated for alpha emitters. Table 3 lists those papers which contained population relevant deterministic endpoints for alpha emitting radionuclides. Finally, Table 4 summarizes the available data on tritium RBE (as HTO), and lists the population relevant endpoints and the test models reported in the literature.

Table 1. Summary of alpha papers on non-human biota (deterministic and stochastic endpoints)

Study	Endpoints	Number of papers*	Test models
In-vitro	Cell Survival	30	C3H10T1/2 mouse cells V79-379A Chinese Hamster Cells, Fischer F344 rats and Swiss Webster mice.
	DNA Damage and DNA Double Strand Breaks	17	Ehrlich Ascites Tumor Cells, C3H10T1/2 mouse cells, V79-379A Chinese Hamster Cells, and Swiss Webster mice.
	Chromosomal Aberrations	12	C3H10T1/2 mouse cells, Chinese Hamster Cells
	Cell Transformations	9	Fischer F344 rats, C3H10T1/2 mouse cells, and Golden Syrian Hamster
In-vivo ex vivo	Effect on haemopoietic tissue	3	Mice (C57B16 and C57B1)
	Tumor Induction	4	Beagles, Mice and Wistar Rats
	Organ/Tissue Effects	3	Rats and Zebrafish

 (*) Represents papers from the open literature published through October 2011. Complete reference citations will be included in the final report of the Task Group.

Table 2. Summary of alpha RBE papers with deterministic and stochastic endpoints.

RBE range	Classification of endpoints		Number of papers*	Test models
	In-vitro	In-vivo/ex-vivo		
>0 - 4	Cell Survival, DNA Damage and Double Strand Breaks, Chromosomal Aberrations and Cell Transformations	Tumor Induction, Organ/Tissue Effects	33	C3H10T1/2 mouse cells, V79-379A Chinese Hamster Cells, Fischer F344 rats and Swiss Webster mice; Beagles, Mice, Wistar Rats and Zebrafish
5 - 10	Cell Survival, DNA Damage and Double Strand Breaks, Chromosomal Aberrations and Cell Transformations	Tumor Induction, Organ/Tissue Effects	24	Ehrlich Ascites Tumor Cells, C3H10T1/2 mouse cells, V79-379A Chinese Hamster Cells, and Swiss Webster mice, Beagles, Mice and Wistar Rats
11 - 20	DNA Double Strand Breaks, and Chromosomal Aberrations	Tumor Induction	4	C3H10T1/2 mouse cells, Chinese Hamster Cells, Beagles, Mice and Wistar Rats
≤25 (+/-8)	Chromosomal Aberrations	Effect on haemopoietic tissue and Tumor Induction	7	Fischer F344 rats, C3H10T1/2 mouse cells, and Golden Syrian Hamster, Beagles, Mice and Wistar Rats

(*) Represents papers from the open literature published through October 2011. Complete reference citations will be included in the final report of the Task Group.

Table 3. Alpha RBE papers with population relevant, deterministic endpoints.

RBE Range	Population relevant deterministic endpoints		LET range, keV/µm	Number of papers*	Test models
	In-vitro	In-vivo/ex-vivo			
>0-4	Embryonic cell, survival/ mortality, Ovary cell survival	Reproductive performance (eg. size of litter, post-natal survival and amount of time it takes female to become sterile), Oocyte Survival, Sperm survival	77-200 100-130*	7	Golden Hamster, Mouse, Male Swiss Webster mice, Chinese Hamster Embryo cells, Mouse Embryo cells, Chinese Hamster.
5-10	Testicular Abnormalities, Embryonic Cell survival /mortality, sperm abnormality.	Testis mass reduction, Oocyte Survival, Sperm Survival	90-142 50-135*	6	Mice (B6CF1), Swiss Webster mice, Golden Syrian Hamster, C3H 10T1/2 mouse embryo.
≤25 (+/-8)	Sperm abnormality	Reproductive effects (Egg production reduction)	130	5	Mice (B6CF1), Zebrafish (Danio rerio), Harvard Swiss Wistar mice

(*) Represents papers from the open literature published through October 2011. Complete reference citations will be included in the final report of the Task Group.

3.2. Overview of findings for tritium

Most of the experimental studies on tritium RBE used tritiated water (HTO) as the low energy beta radiation source, mammals as experimental system and quite high doses (dose-rates) of beta and reference radiation. Few studies have been done with organically bound tritium (OBT), particularly with tritiated thymidine. The experimental data on tritium RBE were classified according to the endpoint analysed in the study., and grouped within one of the four biological endpoints considered relevant at the individual level: mortality, reproductive success, morbidity or chromosomal damage and mutations (ICRP 2008).

Most of these studies were done in mammals (80% of the data), either *in vivo*, with laboratory animals (mainly mice) or *in vitro* (human cells or established cell lines). There is very limited information on tritium RBE in other Reference Animals and Plants (RAPs): 6 tritium RBE values for medaka fish, and single tritium RBE values for insects (Drosophila), plants (*Vicia faba*) and aquatic invertebrates (*Ophryotrocha diadema*). Gamma radiation (from Co-60 or Cs-137) was chosen as the reference radiation more frequently used than orthovoltage X-rays, with 75% of the tritium RBE values calculated in relation to gamma radiation. It is important to note that in all these studies the reference radiation was externally administered while tritium beta particles are internal emitters. Table 4 summarizes the reported RBE for tritiated water. Twenty-nine 29 papers suggest an RBE in the range of 1 to 1.9, 17 in the range of 2 to 2.9, and seven above 3.

Far fewer studies were found relating to organically bound tritium (OBT). Four studies have assayed the RBE of OBT, particularly tritiated thymidine (^{3}HTdR). All but one study has used gamma rays as

reference radiation. The variety of experimental systems used (in vivo or in vitro; different species, developmental stage, cell types), endpoints analysed, and experimental designs used (dose and dose rate ranges, irradiation schedule, reference radiation) makes it very difficult to compare the tritium RBE values obtained in different studies.

Table 4. Summary of tritium RBE for deterministic endpoints (HTO).

RBE range	Population relevant deterministic endpoints		Number of RBE values*	Test models
	In-vitro	In-vivo/ex-vivo		
1.0 - 1.9	Mortality (Embryos, haemato-poietic progenitors, germ cells)	Mortality (mice, fry, beans); Reproductive capacity (fertility and fecundity endpoints); Tissue cell death (spleen, intestinal crypts, thymus)	25 (18 in vivo, 7 in vitro)	Aquatic invertebrate (Ophryotrocha diadema); Plant (Vicia faba); Fish (Medaka); Mouse (Swiss-Webster, CBA/H, ICR, CF1, C57Bl/6, RFM/Nrs); Embryos (Mouse BC3F1, Golden hamster embryos); Cell lines (Murine L5178Y; murine C3H 10T1/2); Human cells (bone marrow)
2.0 – 2.9	Mortality (Germ cells, haemato-poietic progenitors)	Reproductive capacity (germ cells survival); Tissue cell death (Bone marrow, intestinal crypts)	11 (10 in vivo, 1 in vitro)	Mouse (C57Bl/6, RFM/Nrs, Swiss-Webster, DBA2); Fish (medaka); Human cells (bone marrow)
≥ 3.0		Reproductive capacity	1 (In vivo)	Fish (medaka)

 (*) Represents papers from the open literature published through October 2011. Complete reference citations will be included in the final report of the Task Group.

4. INTERPRETATION AND SUMMARY OF DATA

Although most biological effects can be classified as either stochastic or deterministic, there can be substantial variations in RBEs for either type of effect, depending on the particular effect and the biological system under study. As a consequence, judgement is often required in evaluating whether an RBE for a particular endpoint in a particular biological system is relevant to the principle concern in a system of radiological protection of non-human biota, for example maintaining the viability (reproductive capability) of populations of the most sensitive species in radiological protection of the environment.

It should also be noted that at least for some endpoints such as circulatory disease or damage to the lens of the eye, the same threshold has been proposed for acute, and either fractionated or protracted

(chronic) doses. This therefore blurs, somewhat, the distinction between stochastic and deterministic effects.

Overall, the data indicate that RBEs for high-LET radiations in inducing deterministic effects generally are lower than RBEs for those radiations in inducing stochastic effects. For example, at low doses of interest in radiological protection, the reduction in RBEs for deterministic effects induced by alpha particles and fission neutrons compared with RBEs for stochastic effects appears to be about a factor of 2 to 3 (ICRP, 1990; Kocher and Trabalka, 2000).

It was surprising how few papers were available to calculate RBE_m and RBE_M. It was not as unexpected that the number of papers containing endpoints directly relevant to protection of populations was small. It was noted that the difference in RBE_m vs. RBE_M was not as substantial as expected from previous reports in the literature.

5. CONCLUSION

This presentation provides a summary of on-going efforts to develop a logical, transparent, and defensible approach to establishing radiation weighting factors for use in assessing impact to non-human biota. The work discussed in this paper provides an overview of the range of RBE values for alpha particles and tritium that appear relevant in the context of protection of the environment from ionising radiation. The data suggests that nominal dose modifying factors for alpha emitters lie in the range of 10. The value for tritium continues to undergo review and discussion. Finally, the distinction between stochastic and deterministic radiation effects becomes less clear in the context of radiobiological studies relevant to the protection of plants and animals.

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