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Low doses and non-targeted effects in environmental radiation protection; where are we now and where should we go?

Carmel Mothersill*, Andrej Rusin, Colin Seymour

Medical Physics and Applied Radiation Sciences, McMaster University, Hamilton, Ontario L8S 4K1, Canada

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ABSTRACT

The field of low dose radiobiology has advanced considerably in the last 30 years from small indications in the 1980's that all was not simple, to a paradigm shift which occurred during the 1990's, which severely dented the dose-driven models and DNA centric theories which had dominated until then. However while the science has evolved, the application of that science in environmental health protection has not. A reason for this appears to be the uncertainties regarding the shape of the low dose response curve, which lead regulators to adopt a precautionary approach to radiation protection. Radiation protection models assume a linear relationship between dose (i.e. energy deposition) and effect (in this case probability of an adverse DNA interaction leading to a mutation). This model does not consider non-targeted effects (NTE) such as bystander effects or delayed effects, which occur in progeny cells or offspring not directly receiving energy deposition from the dose. There is huge controversy concerning the role of NTE with some saying they reflect "biology" and that repair and homeostatic mechanisms sort out the apparent damage while others consider them to be a class of damage which increases the size of the target. One thing which has recently become apparent is that NTE may be very critical for modelling long-term effects at the level of the population rather than the individual. The issue is that NTE resulting from an acute high dose such as occurred after the A-bomb or Chernobyl occur in parallel with chronic effects induced by the continuing residual effects due to radiation dose decay. This means that if ambient radiation doses are measured for example 25 years after the Chernobyl accident, they only represent a portion of the dose effect because the contribution of NTE is not included.

1. Reason for this review and discussion

This review was prompted by the realisation that there are two major disconnects which impact the current discussions of how to develop radiation protection frameworks for non-human species. The first is that radiobiologists and radioecologists seldom interact and their areas of interest do not really overlap. The second is that radiation protection of non-human species has employed the concepts of "reference man" from human radiation protection when it might be more useful to use concepts developed in environmental protection fields where concepts of ecosystem and population effects dominate rather than the current focus on "reference organisms". The aim of this discussion paper is, therefore, to explore some areas of radiobiology which might help in the conceptual and experimental development of more useful ways to enable protection of non-human biota

2. Description and history of the paradigm shift

Up until the 1980's radiobiology was a DNA-centric science (Hall and Giaccia, 2006). DNA was regarded as the critical target and DNA strand breaks the critical lesion. DNA damage was either repaired successfully or not repaired in which case the cell died or perpetuated a mutation to all of its offspring. If this mutation happened to be in a cancer-associated gene, a cancer could arise (Hall and Giaccia, 2006). The clonal origin of cancer theory dominated and little thought was given to the micro-environment or the idea of niches (Suzuki and Yamashita, 2012; Chang et al., 1982). Much of the radiobiology research going on then was focussed on understanding DNA repair mechanisms and through understanding individual cell survival, research was aimed at manipulating response of individual tumour cells to radiation with the aim of controlling cancer (Hall and Giaccia, 2006). Tools were not really available to investigate low dose effects and anyway these were deemed irrelevant for cancer therapy. How this domination of the field came about is an interesting question for science historians because prior to about 1950, there was considerable discussion of indirect effects (what we now call non-targeted effects) and the existence of other "targets" for radiation energy deposition was widely discussed (Bonnier, 1952; Devik, 1953; Mole, 1953). After the

* Corresponding author.
E-mail address: mothers@mcmaster.ca (C. Mothersill).

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discovery of the structure of DNA, the "inconvenient truths" which did not fit the paradigm were ignored or deemed to be irrelevant to the mechanisms which resulted in DNA defects (Nomiya, 2013).

Several things drove the paradigm shift in the late 20th C. These included advances in molecular biology which allowed effects of low doses to be studied, the Chernobyl accident in 1986 and subsequent concerns about low dose effects and about nuclear power in general. These resulted in funded research into low dose effects by governments and industry alike. The key thing was however, the publication of a series of papers in the late 1980's and early 1990's which suggested that "indirect" mechanisms had very profound effects (at least in laboratory experiments) on the shape of the low dose region of the radiation dose response curve (Seymour et al., 1986; Pampfer and Streffer, 1989; Kadhim et al., 1992; Nagasawa and Little, 1992; Mothersill and Seymour, 1997a, 1997b)). These papers challenged two fundamental assumptions; one was that all radiation damage was fixed (in the sense of being made permanent) in the first cell division post irradiation and the second was that irradiated cells acted independently of each other. The very important consequences of these two conceptual changes were that time post irradiation became important and population effects or environmental status was recognised to play a part in determining outcome. Fig. 1 is an attempt to compare the old and new paradigms.

3. Components of the NTE type of effect

The term "non-targeted effect" (NTE), strictly speaking, means effects in cells, tissues, organs or organisms which received signals from irradiated systems but did not necessarily receive a direct deposition of energy from ionising radiation. Generally they include genomic instability/delayed lethal mutations where radiation damage is detected in distant progeny of cells which survived the initial exposure and appeared healthy for multiple generations and bystander effects where effects are seen in neighbours which did not receive any direct dose. Signalling can also impact neighbours which did receive a direct hit but for the purposes of this paper, it is assumed that the effects are detected in progeny or unirradiated neighbours. Other effects such as adaptive responses and low dose hypersensitivity are more properly described as low dose effects but are often included in discussions of NTE. These effects have all been extensively reviewed over the last 30 years (e.g. Mothersill and Seymour, 2012; Burtt et al., 2016) and this review will focus more on the relevance of these effects for environmental radiation protection than on the actual mechanisms of NTE. Key features of these effects which are relevant are that they appear to have an "on/off" threshold in the low mGy dose range (Schettino et al., 2003, 2005; Liu et al., 2006, 2007). The effect saturates after an acute low LET exposure of about 500 mGy (Seymour and Mothersill, 2000; Prise et al., 2002,) and once triggered, the effects persist over time and are trans-generational both in cell cultures and in vivo (Lyng et al., 1996; Lorimore et al., 2001; Kashino et al., 2004; Coates et al., 2008). They have been detected across all taxonomic groups tested (O'Dowd et al., 2006; DeVeaux et al., 2006; Bertucci et al., 2009; Audette-Stuart and Yankovich, 2011; Sharetskiĭ et al., 2012; Fernandez et al., 2016; Smith et al., 2016), and signals can cross species boundaries meaning signals generated by one species can induce responses in unrelated taxonomic groups often separated by millions of years of evolution (Smith et al., 2013; Hatzi et al., 2015,). The consensus is that they represent a very primitive, highly conserved stress response which may coordinate response to environmental stressors, experienced by individuals, to produce higher level outcomes at the population or ecosystem level.

The question is whether this in any way impacts responses of non-human biota to radiation exposure and whether these effects need to be integrated into risk models for environmental radiation protection?

4. Dominance of direct effects in protection science

Currently only direct effects of radiation are considered relevant (UNSCEAR, 2008). This applies to theoretical or modelling efforts, to epidemiological analyses, which are deemed to include any NTE if relevant and to human science based investigations. These three areas will be considered briefly below

4.1. Theoretical modelling

Modelling efforts to try to predict the shape of the dose response curve in the low dose region generally use the large human cohorts of the A-bomb survivors or the Techa River residents (Dropkin, 2016; Preston et al., 2016). Modelling in the non-human biota field uses the Frederika database (Vives I Batlle et al., 2012). A few attempts have been made to factor NTE into the human models but these have assumed NTE are harmful which may not always be the case (Little, 2004;

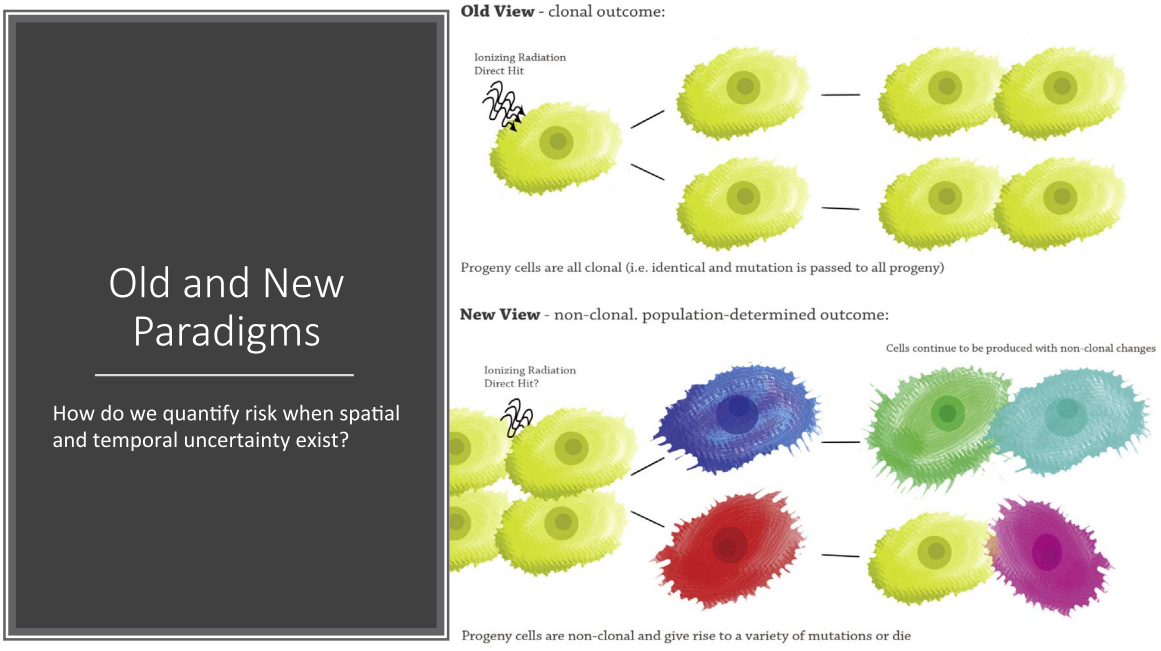

Fig. 1. Conceptual representation of the old and new paradigms of radiation action at low doses.

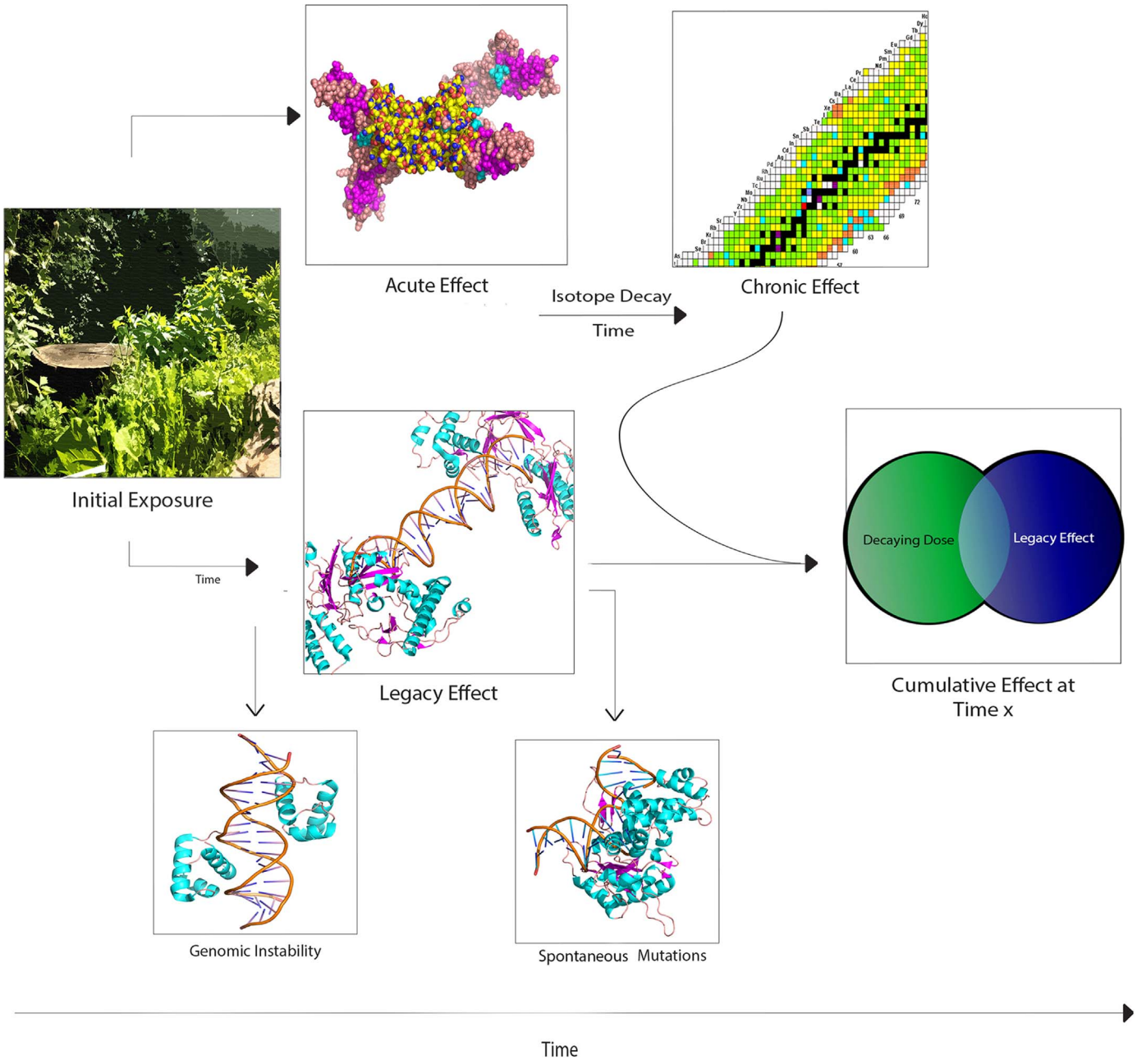

Fig. 2. Conceptual approach to the resolution of the separate contributions of Initial dose, genomic instability contribution (legacy effect) and attenuating chronic dose to the effect burden at any given time.

Kundrát and Friedland, 2015).

4.2. Epidemiological

Human epidemiological studies, have weak power at doses below 100 mGy because the numbers of subjects needed to detect excess incidence of common diseases such as cancer exceeds the size of the cohorts available (Averbeck, 2009; Preston et al., 2013). With wildlife similar problems exist and the concept of "wildlife epidemiology" is more properly referred to as field studies. The consideration of these is outside the scope of this discussion but important contributions to the discussion of persistent genetic or chromosomal damage include those of Moller, Mousseau and colleagues whose extensive studies report mutation effects at very low doses and who also consider long term adaptation of populations in Chernobyl and Fukushima to chronic irradiation (reviewed in Møller and Mousseau, 2015, 2016 and Einor et al., 2016). Other long term genetic studies have been done by Goncharova and colleagues in Belarus on multiple generations of bank voles (Goncharova and Ryabokon", 1998; Goncharova and Smolich, 2002; Ryabokon and Goncharova, 2006). The idea of factoring in historical doses which could exert an influence via NTE does not seem to have been considered for humans or wildlife. The concept of a "memory effect" has been put forward but does not appear to have been published or formalised.

4.3. Science based laboratory and experimental studies

These studies set up very carefully controlled experiments in the lab or the field, with the aim of determining dose response relationships for cancer, reproductive impact or other defined endpoints. The problem with such studies is that they generally use doses above those of concern in the environment or in human radiation protection mainly

because lower doses do not produce effects in a reasonable time frame. While long-term experimental studies do exist for example the mega mouse or beagle dog experiments (Haley et al., 2011) or in the environment, the Colorado, some Chernobyl studies and the AECL Manitoba experiments (Reichle et al., US on-line link, Mihok, 2004; Audette-Stuart et al., 2011; Geras'kin, 2016,) these are limited both in the type of radiation used, the species or habitat studied and the endpoints measured. However they provide the best chance of determining direct dose response relationships in a controlled way. Indirect effects such as genomic instability, adaptive response, low dose hyper sensitivity and bystander effects have been exhaustively studied in experimental models for humans and in laboratory species of non human biota including plants but there is no agreement about what the data mean for radiation protection (Morgan and Sowa, 2009; Mothersill and Seymour, 2014). This is mainly because these effects have not been definitively linked to health outcomes.

5. What would happen if we included NTE? Would it really increase uncertainty?

A key factor prompting caution from radiation protection bodies such as ICRP and scientific committees such as UNSCEAR or BEIR who evaluate scientific data, is the lack of any clear mechanism such as a signature mutation linking NTE with detrimental health effects. Much of the research into NTE has been done using cell cultures or inbred rodent strains which are known to be susceptible to cancer and are used as models to study mechanisms of carcinogenesis (e.g. Attardi and Donehower, 2005), cardiovascular disease (Ginsberg and Busto, 1989) or neurodegenerative disease (Shukla et al., 2015). The few whole animal or plant studies looking at low dose NTE endpoints do not follow through to inform about health endpoints of interest in environmental radiation protection such as fertility or fecundity. It is true that NTE such as the bystander effect induce genomic instability in progeny of unirradiated cells receiving signals from irradiated cells (Seymour and Mothersill, 1997; Lorimore et al., 1998; Bowler et al., 2006) and since genomic instability is a hallmark of cancer, the argument is made that NTE could underlie or contribute to carcinogenesis after low dose exposure (Ponnaiya et al., 2011; Klammer et al., 2015; Hei, 2016). Similarly signalling aberrations or disruptions could also lead to neural or immune system compromise especially since once turned on NTE do not appear to fade or disappear with time (Marozik et al., 2007; Koturbash et al., 2007; Buonanno et al., 2011). It is unlikely that building NTE components into models would increase the uncertainty over what it is already. In fact inclusion of a factor to account for persistent effects due to historical radiation exposure might actually help explain some of the variability in results seen in the field because it would allow total effect to be calculated as the sum of the effect due to ambient or current dose plus the effect which can be currently measured which occurs due to the historic legacy effect (genomic instability effect) of the initial exposure. Fig. 2 is an illustration of this concept.

5.1. Relative contributions of adaptive response and adverse destabilising effects

A major difficulty in this field results from the fact that bystander signals and even genomic instability are not intrinsically “bad”. Genomic instability can provide material for natural selection by increasing genetic variability. This can lead over the long term to adaptive responses and a fitter population more able to withstand the new environmental stressor. Bystander signalling has been shown to enable communication of a stress response between organisms which could in theory at least lead to pre-emptive upregulation of defensive mechanisms (Szumiel, 2015). However the issue for radiation protection is sorting out the relative contribution of good or bad outcomes to the overall population or system which has been exposed. It is likely that novel modelling approaches will be needed to make progress in this area. Fig. 3 depicts 2 extreme scenarios. In Scenario 1 there is no adaptation and the historic dose effect is constant for each population doubling with no compensation for the reduction in survival of progeny. This means that at each population doubling the number of progeny is reduced by a constant factor due to the historic dose and eventually extinction of the population will occur. In Scenario 2, the system compensates by increasing the growth rate or otherwise acting to maintain the population at or above the level that initially survived the direct dose.

6. Individual variation and “confounding factors”

A further issue which is relevant to the question of what would happen if we included NTE in radiation protection risk estimates is individual variation. In human populations this includes genetic and lifestyle factors which change the radiosensitivity of an individual to direct irradiation or NTE (Coen et al., 2001; Glaviano et al., 2006; Mothersill et al., 2014). In non human species, these factors will also impact radiation sensitivity but will be more difficult to identify and control. As they will operate at the population and ecosystem level, it is likely the effects will be buffered or neutralised but could contribute to population drift and structural polymorphism.

6.1. Multiple stressors

No species exists in a pure environment therefore the issue of multiple stressors is relevant to low dose radiation protection. This is especially true of NTE because they manifest as a stress response and can be induced by chemical and other physical conditions/pollutants as well as radiation (Salbu et al., 2005, 2008; Mothersill et al., 2007,). A further complicating factor is that since NTE saturate after quite low doses, the additional effect of extra stressors may be negligible in terms of NTE but may augment or reduce direct effects through synergistic or antagonistic interactions. Again modelling approaches may help regulators make predictions in well characterised contaminated sites.

6.2. Role of response modifiers

This category of agents is related to the last in that it includes physical and chemical modulators of radiation or other stressor effect. These agents act to modulate responses induced by the multiple stressors including radiation. They include mitigators of radiation damage such as antioxidants (Asur et al., 2010; Smith et al., 2015). However again the effect of mitigators may be on direct damage, NTE damage or both. It is important to consider relevant mechanisms of action in order to predict what effect if any mitigators might have on NTE.

7. Need for system level conceptual analysis

Probably the single most important need identified in this part of the review is that in order to determine what NTE might do to current approaches to radiation protection of the environment or of humans, is the need to consider the issues at the level of the ecosystem or population. The concept of NTE expands the area affected by direct radiation exposure both temporally (vertical transmission to progeny) and spatially (horizontal transmission to neighbours). This means that the response of the system cannot be deduced from knowledge of dose, hit cells or hit individuals. System level modelling is required and system level indicators of radiation effects are needed. Attempts to develop such a conceptual framework are underway (Mothersill and Seymour, 2010; Bradshaw et al., 2014; Bréchignac et al., 2016 and b) and may ultimately require borrowing of models from economic forecasting and disaster forecasting fields.

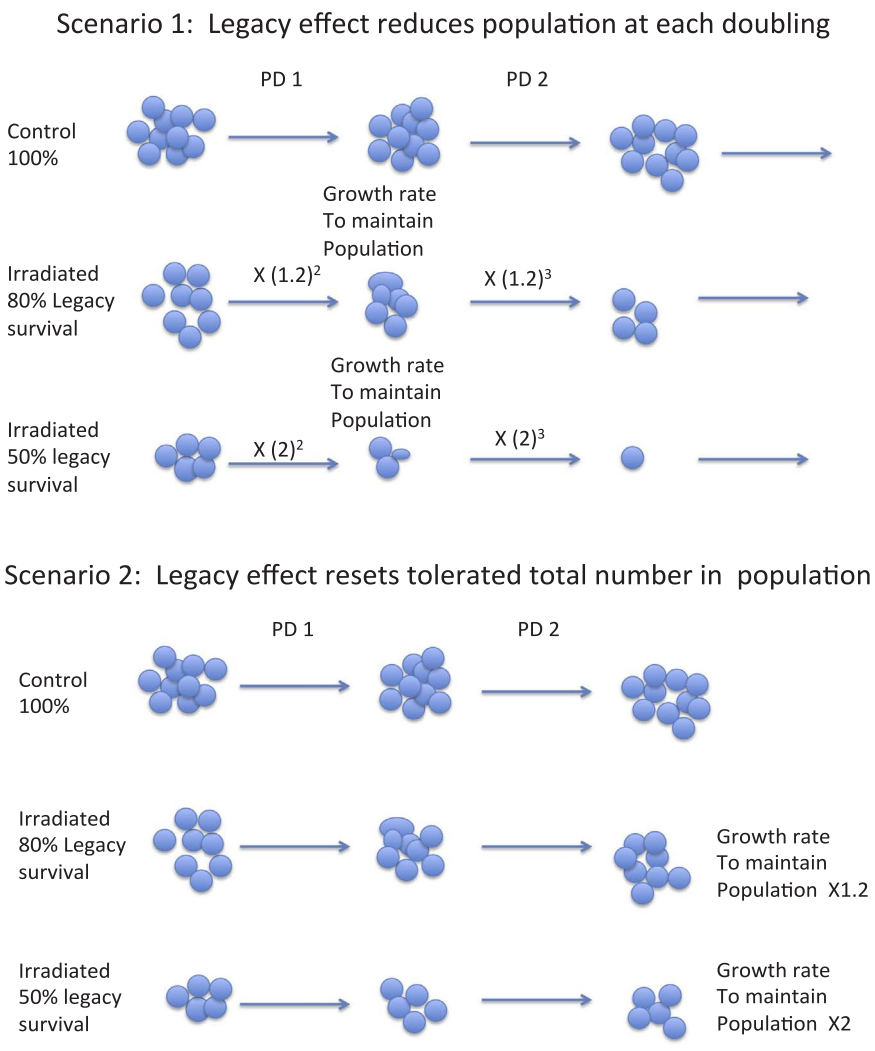

Fig. 3. Extreme scenarios of how historic dose could impact population survival where no adaptation or compensation occurs (Scenario 1) or adaptation does occur (Scenario 2).

8. Practical ways forward

Two approaches to developing system level frameworks of protection are obvious. One involves actual measurements in field situations, where health of ecosystems (using such metrics as biodiversity index or stability of population numbers over time) can be monitored in relation to ambient and historical dose. The problem is establishing good controls to cover the impacts of other natural and anthropocentric stressors. The determination of accurate doses is also problematic given the complex chemistry and speciation, which make interpretation of the likely impacts of measured doses difficult. Contributions of "hot particles", microparticulates and nanoparticulates are hotly disputed and may contribute to local and internal doses (Garger et al., 2013; Tyler et al., 2013; Beresford et al., 2016a, 2016b). In terms of estimating contributions of historical doses, the only obvious experimental approaches are to extrapolate from relevant in vitro or ex-vivo studies which use an appropriate range of doses and isotopes or to use data from the very few field studies which measured biological effects in populations over time. These data then need to be combined with theoretical interpolation of historic dose–effect predictions based on existing knowledge of the relative contribution of historic and ambient doses to the cumulative effect. These experimental approaches still leave the problem of how to measure impacts at the level of the ecosystem when actual measurements have to be done on individuals within ecosystems. The other type of approach is conceptual or theoretical, involving modelling. Currently, this is an area of intense effort (Yankovich et al., 2010; Alonzo et al., 2016; Beresford et al., 2016a, 2016b) but it is unknown how useful it will be given the huge gaps in the databases concerning all but the most commonly used animal models and the preponderance of acute low LET data when high LET, chronic exposure contributes much to the total dose in Chernobyl, Fukushima and other exposure sites such as the legacy test sites and uranium mining areas. The other problem with modelling using database information is that much of it concerns measurements on individuals using toolboxes which were considered important and which may have been surpassed by more modern tools. For example genomic screening, chip technologies and network analyses can generate vast amounts of information but was not applied to most of the large radiation studies. Another issue with modelling is that the parameters have to be preselected and since we do not know what is important in determining ecosystem level outcomes, it is hard to know what terms to include. It is possible that some of the so-called "wicked problem" uncertainty models used in banking and economic forecasting mentioned above may be worthy of consideration. These models accept that we do not know what elements drive the effect or the response and use a form of complexity modelling to allow uncertainty to be accommodated in the models.

9. Conclusions and summary

This paper set out to consider the impact that modern thinking about low dose radiobiology might have on environmental radiation protection regulation. The conclusions are that in the low dose/dose rate range, effects are not solely determined by absolute absorbed dose

but are modulated by many factors meaning they are context dependent. Beneficial and adverse effects can occur and it is difficult to predict what will happen, particularly in complex systems with multiple variables. Non-targeted low dose effects mean that spatial and temporal contexts need to be considered in addition to snapshot measurements in individuals. The value of existing experimental and theoretical approaches is examined and a major conclusion of this analysis is that new approaches are badly needed, possibly borrowing techniques from economic forecasting. The quite surprising overall conclusion is that NTE which came from human radiation biology are probably much more important in environmental radiation biology because of their relevance and role at the level of the population and ecosystem.

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