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

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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

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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;

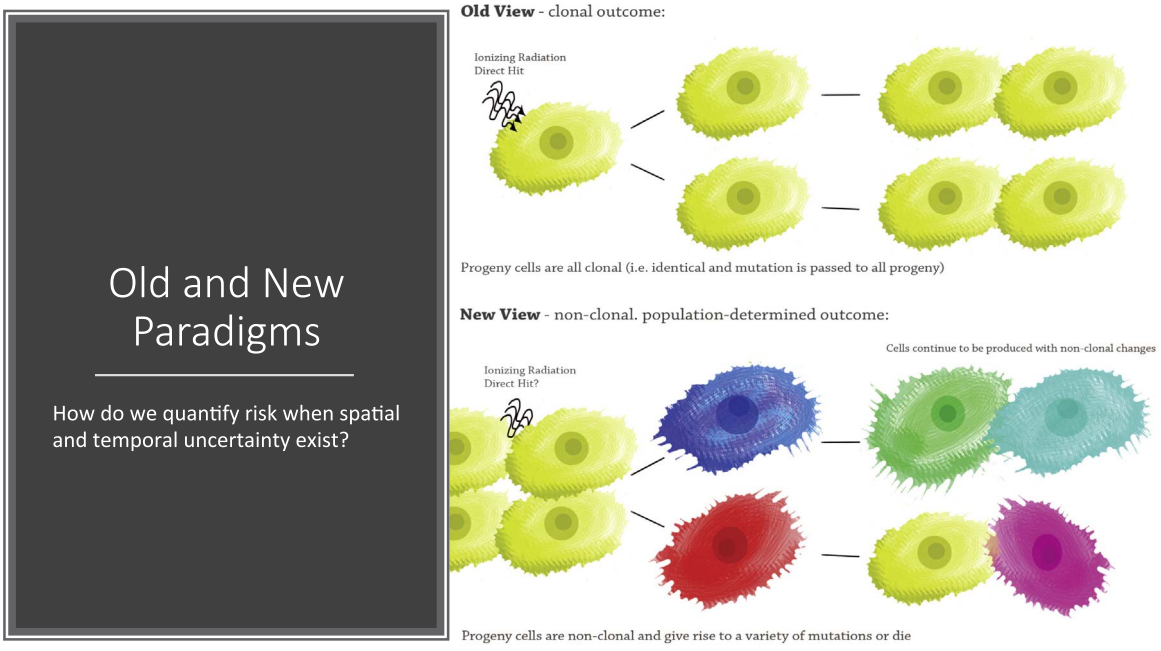

Fig. 1. Conceptual representation of the old and new paradigms of radiation action at low doses.