Radiation Protection of Biota; New concepts to consider

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Concepts in the low/chronic dose(rate) field which may be important

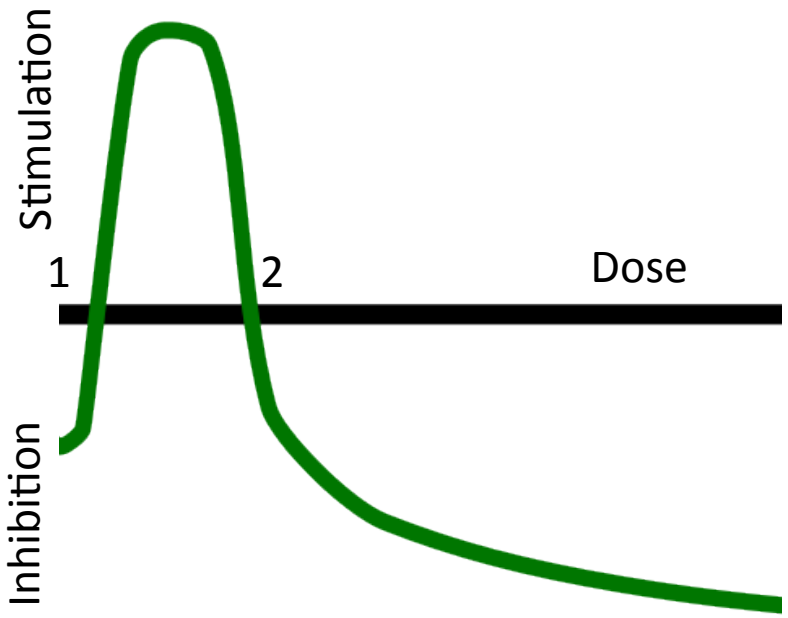
- Hormesis/Adaptive responses
- Spectrum of responses
- Low doses different (NTE dominate response)
  - Genomic instability
  - bystander effects
  - hypersensitivity
- Translation across species
- Molecular markers and system biology

Hormesis

Definition and importance

- Stimulation of the system by low dose/dose rate exposure which becomes harmful as the dose increases
- Important because it provides 2 “no effect levels” in the dose response curve but the dose(rate) at which stimulation occurs is highly variable and depends on multiple factors
- Also important because hormetic doses are often in the range of environmental concern!

Shape of curve



Modelling Hormesis

- A multi-criteria weight of evidence approach for deriving ecological benchmarks for radioactive substances

J Garnier-Laplace, C Della-Vedova, P Andersson, D Copplestone, C Cailes, N A Beresford, B J Howard, P Howe and P Whitehouse

J. Radiol. Prot. 30 (2010) 215–233

Deliverable from PROTECT

During PROTECT, new data imported into FREDERICA were processed in a similar way and the mathematical treatment was enlarged to include data sets exhibiting a hormetic pattern. All data sets in FREDERICA can be fitted to either logistic or hormetic models

Calculation of SSD for a generic ecosystem

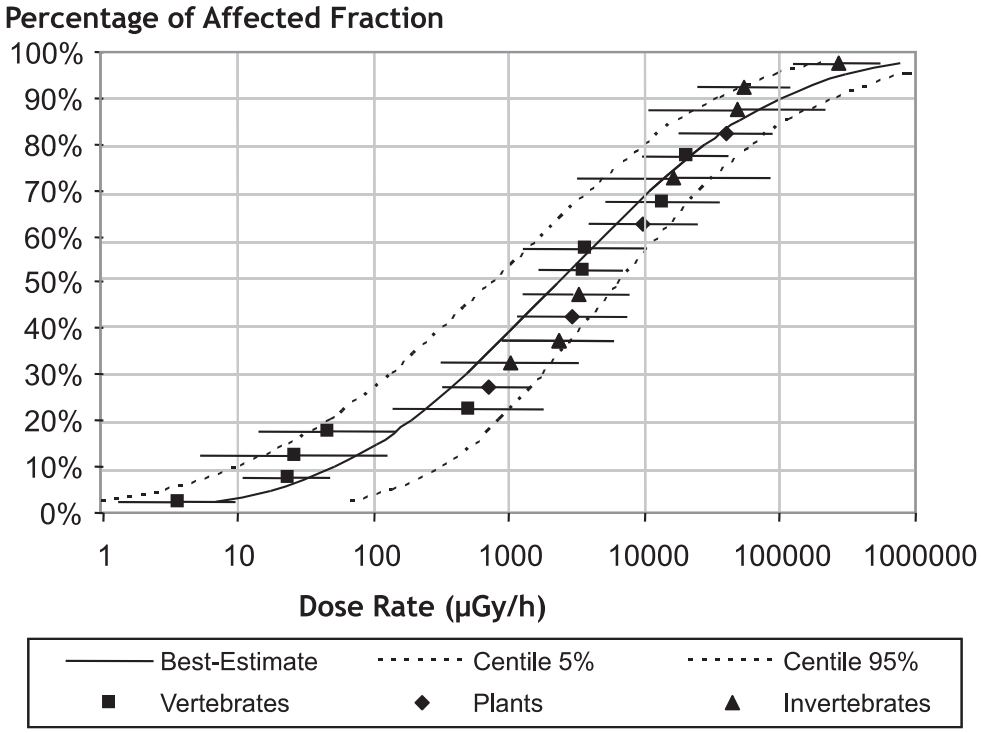


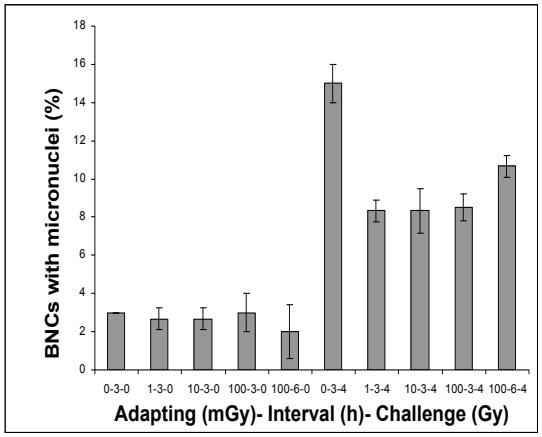
Figure 3. Species sensitivity distribution for generic ecosystems (freshwater, marine or terrestrial) and chronic external gamma exposure conditions. The log-normal distribution is fitted to the set of lowest EDR_{10} values (20 data which are the lowest per species). The estimation standard error is represented by horizontal bar for each EDR_{10}.

Adaptive Responses

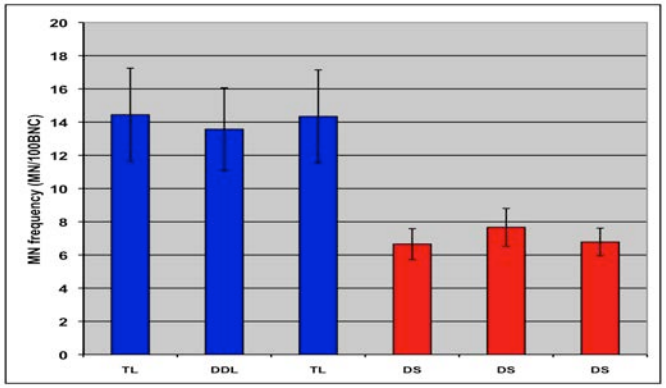
Definition and Importance

- Resistance to a large dose induced by exposure to a very small or chronic dose
- Important because it renders the dose response relationship non linear
- Implications for pristine v contaminated environments as cross adaptation is common.
- Individual (species?) variation in level or existence of response adds to uncertainty

Typical data sets



mGy acute dose followed 3h later by 4Gy acute dose



All frogs exposed to 4 Gy in the laboratory (liver cells exposed in vivo).
Blue: Cells from frogs from background sites (DDL and TL)
Red: Cells from frogs from above background site (DS)

Arguments why it is NOT important

- RP is conservative and as long as we are not risking harm it is OK so adaptive or hormetic effects are irrelevant
- We do not know the relevance of endpoints such as DNA damage or micronuclei to reporductive or mortality endpoints in populations

BUT

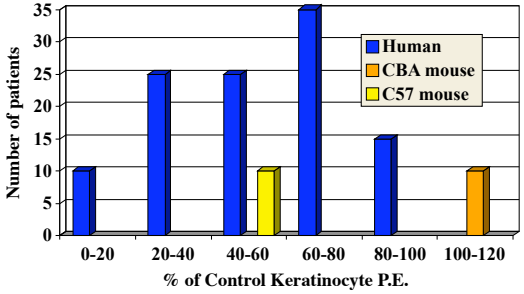
- Need to look at the big picture
- If we can reduce uncertainties and factor in adaptive effects, nuclear might be a really good option to reduce climate change while maintaining lifestyle
- Uncertainties in low dose region include potentially harmful effects including genomic instability, low dose hyper-radiosensitivity and micronuclei. These may act as early warning signs of system perturbation

Spectrum of responses

Why is it important

- Most lab models are inbred strains but in the field individuals vary
- Factors other than dose may dominate outcome – e.g. food supply, health, other stressors
- May need to model range rather than average

Typical data sets



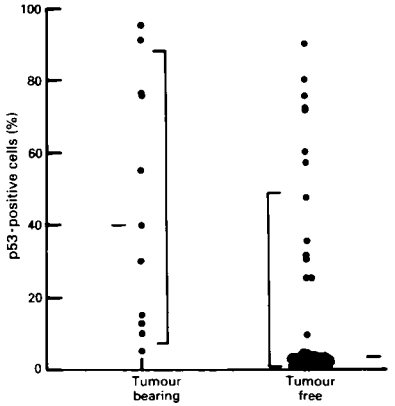


Figure 3 Percentage of normal urothelial cells stained positive for p53 protein following 14 days in tissue culture from tumour-bearing ($n = 11$) and tumour-free ($n = 60$) patients. $P < 0.0005$, d.f. = 69. The medians and interquartiles are indicated on the graph.

Low dose(rates) are different

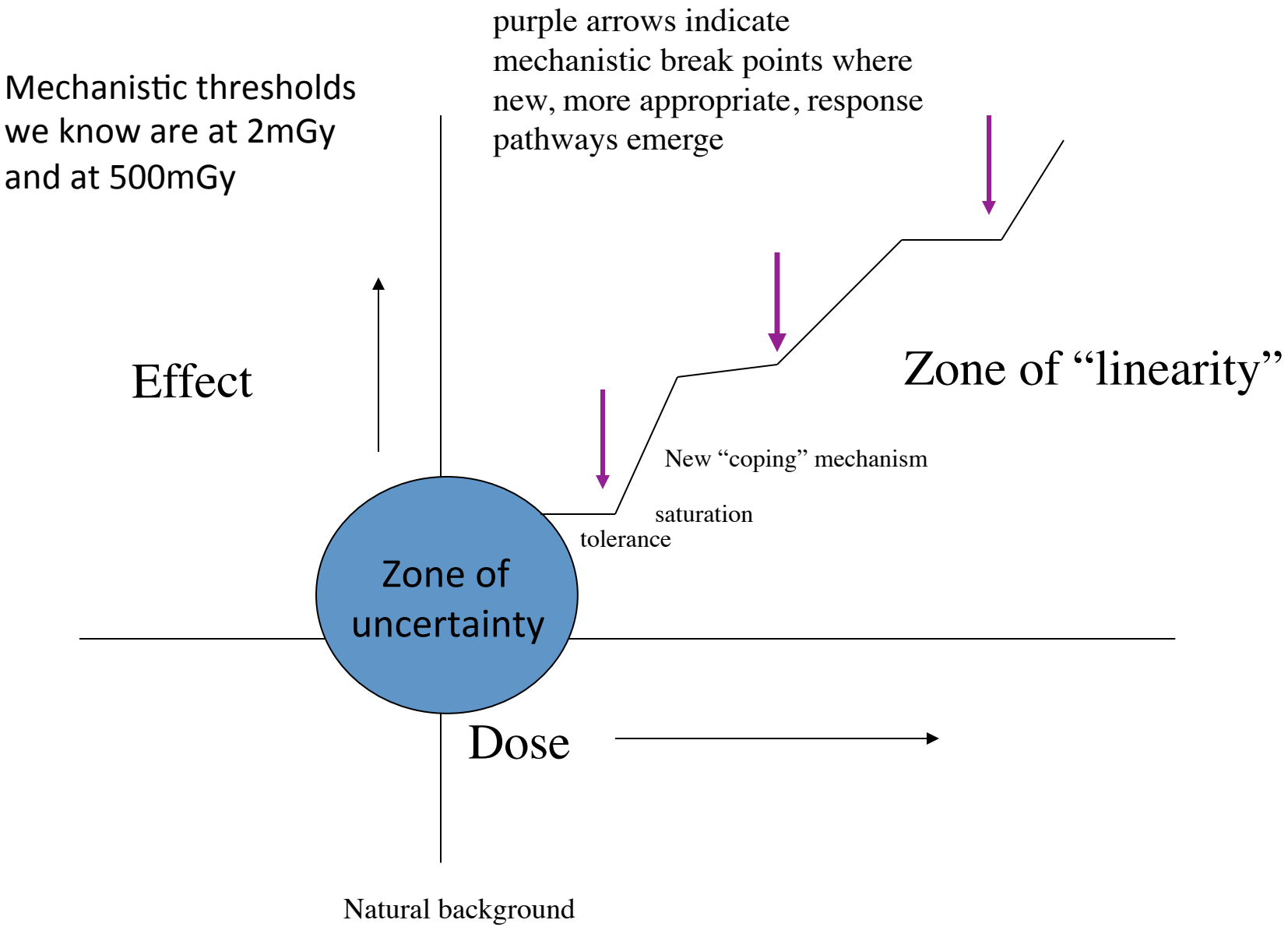
Why is this important?

- If we assume we can extrapolate from high doses where we have lots of data we may be looking at the wrong things
- Generation of biomarkers and benchmarks requires some understanding of relevant mechanisms

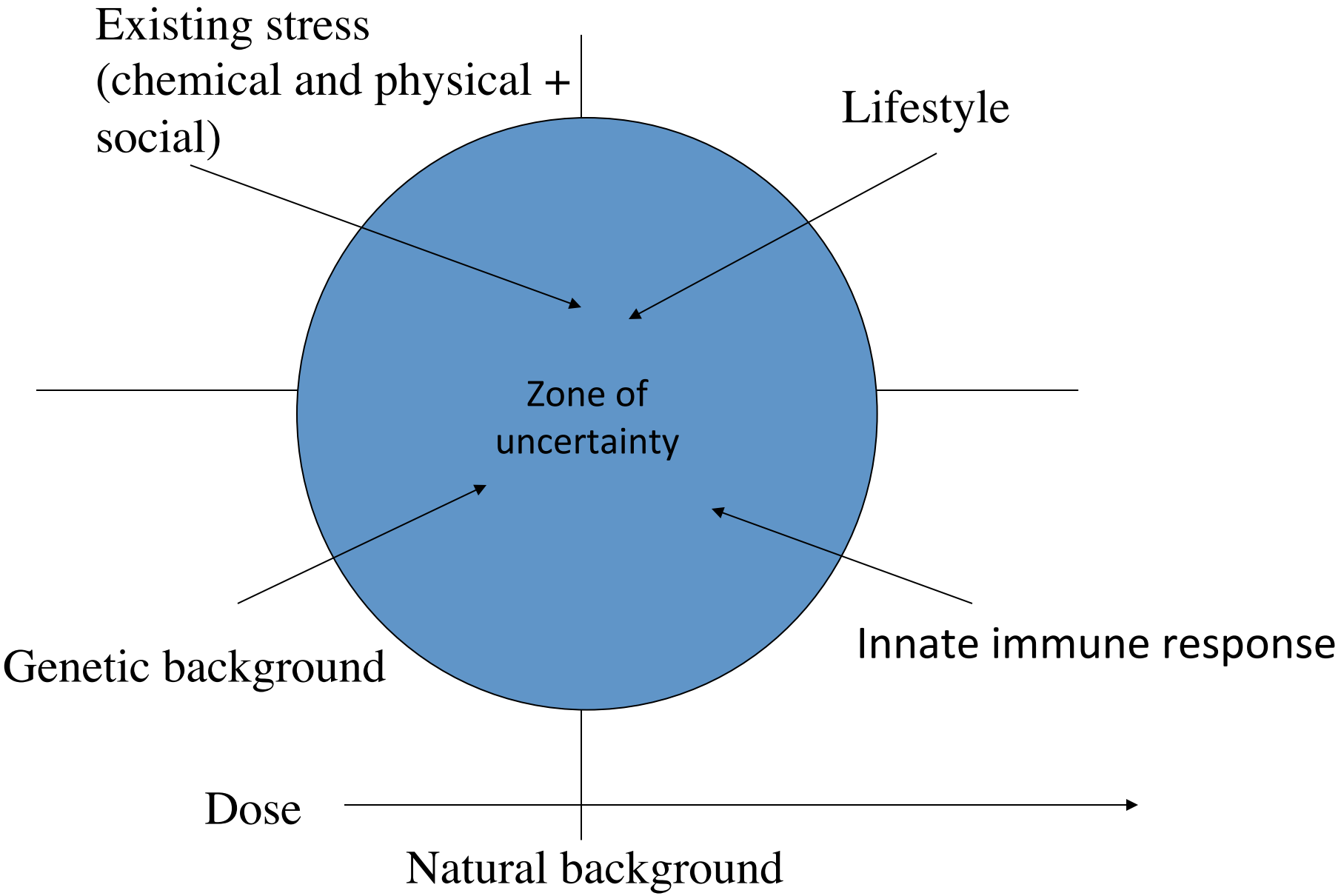
Evidence

- Non linearity common in dose response curves
- Low dose hyperradiosensitivity is an example
- Non-targeted effects dominate at low doses and have discontinuous dose responses
- Uncertainty much greater after LDRIR and LDIR

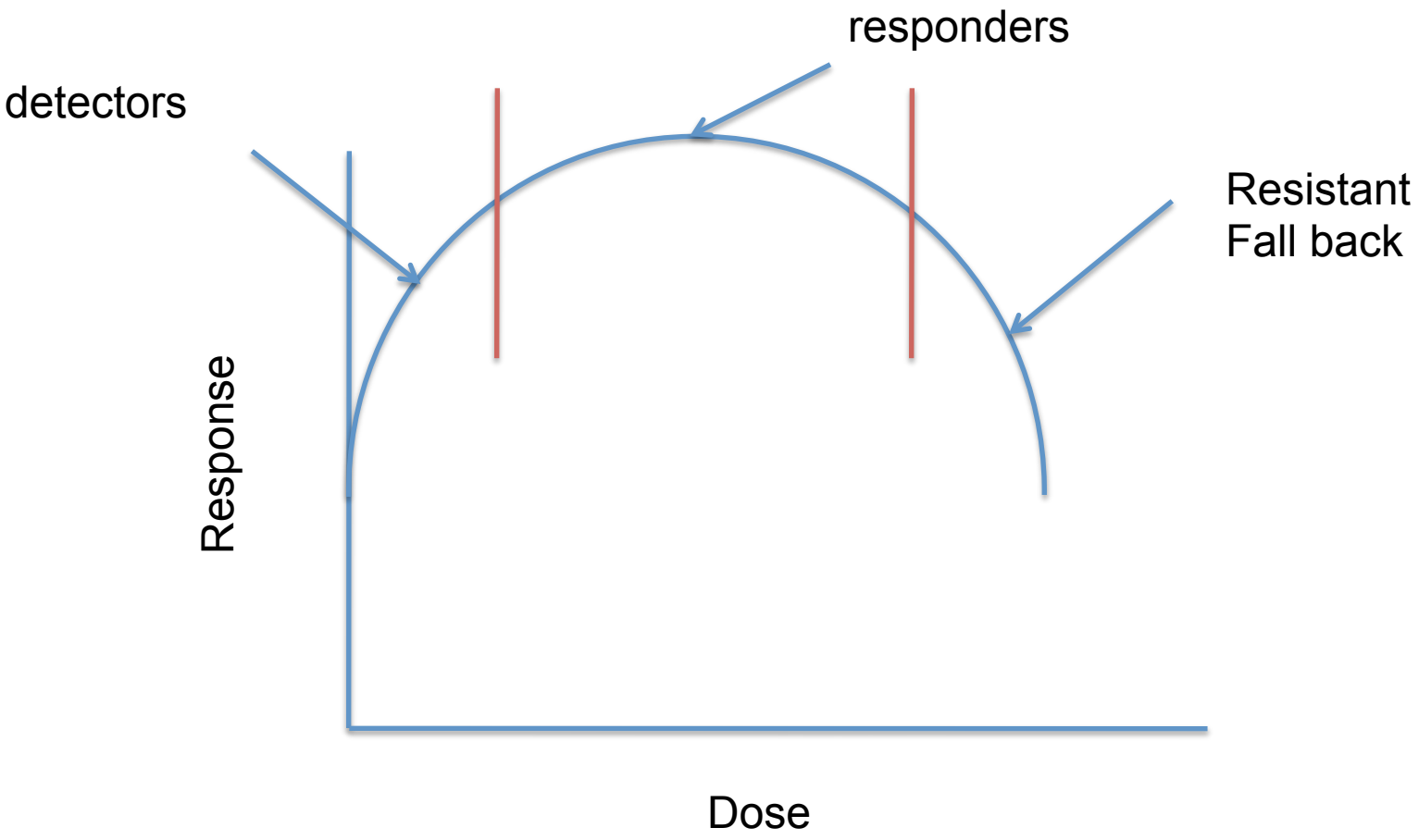
Proposed dose response relationship for radiation-induced effects



Factors influencing outcome in the zone of uncertainty



Concept of first responders/reactors which are very sensitive to the stressor and alert others



Translation across species

Why is it important

- Impossible to get indicators for all species but robust indicators from other fields of radiobiology might translate across species
- Models in human radiobiology include rodents, zebrafish and nematodes.
- These might give pointers about what to look for
- Classic indicators such as reproduction and mutation are blunt tools in the low dose range

Possibly useful indicators

- Stress biomarkers such as MAPK, ROS etc
- Indicators of DNA damage such as γH2AX
- Indicators of apoptosis such as cmyc or BAX
- Non-targeted effects such as bystander signaling or genomic instability (best hope for population level markers)

Non-targeted effects; population level coordination of response?

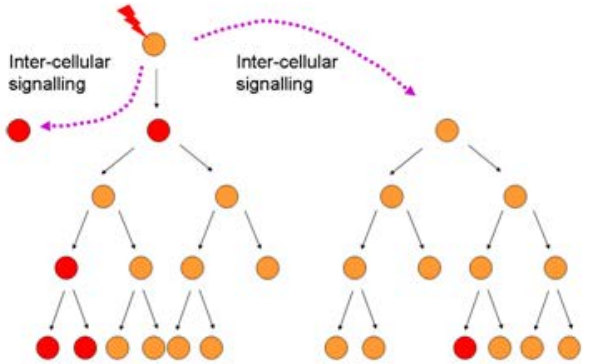
'Non-targeted' radiation effects

Bystander effects

Effects in neighbouring cells

Genomic Instability

Effects in unirradiated descendant cells

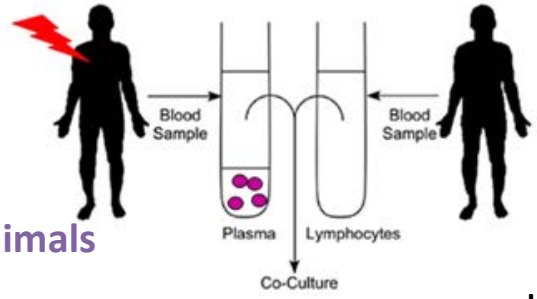


Abscopal effects

Effects in neighbouring tissues

Clastogenic factors

Ex vivo effects in cultured cells



Inter-animal signaling

Effects in neighbouring animals

Inflammatory Processes may provide mechanistic link

Long-term effects on innate immune response function may occur

Important points about NTE

- Dominate low dose response
- Deterministic effect with threshold of about 2mGy (acute low LET). High LET unknown
- Binary response (cells in population do or do not show response)
- Means mechanism is fully active and producing effects in the dose region considered too low to be a problem (less than 100mGy)
- Genetic basis for response and masked/ inactivated by certain chemicals and by presence of cancer

In vivo communication of signals

- Surinov: irradiated mice become unattractive to potential mates due to secretions in the urine 2002 -
- Seymour/Mothersill: Irradiated fish communicate to unirradiated swim buddies and all respond as if irradiated (bystander effect in vivo) 2006 -
- Audette-Stuart: Tadpoles from tritium contaminated water convey signals to unexposed tadpoles so they respond as if adapted 2011-

NTE's allow multiple outcomes – facilitate adaptive responses and evolution

- GI opens up the chance for change and adaptive or mal-adaptive evolution similar to stress induced mutagenesis in bacteria
- Bystander effects signal between hierarchical levels to coordinate responses at different organisational levels?
- GI + BSE allow spatial and temporal system control but…
- in any system change only favours a few


Reproductive and transgenerational effects
Acute and chronic data

Reproduction in ^{226}Ra treated fish and mice

- Chronic feeding with radium spiked food. No indication of any impacts on reproduction or egg viability of the environmentally relevant doses tested in zebrafish or fathead minnows. No effects reproductive effects at all in mice out to F_4 generation.
- Impacts in fish appear to be epigenetic. They are present in the generation actually exposed and appear to transfer to F_1 but not to F_2. Include effects on growth rate and biochemical indices.

In vitro radium experiments

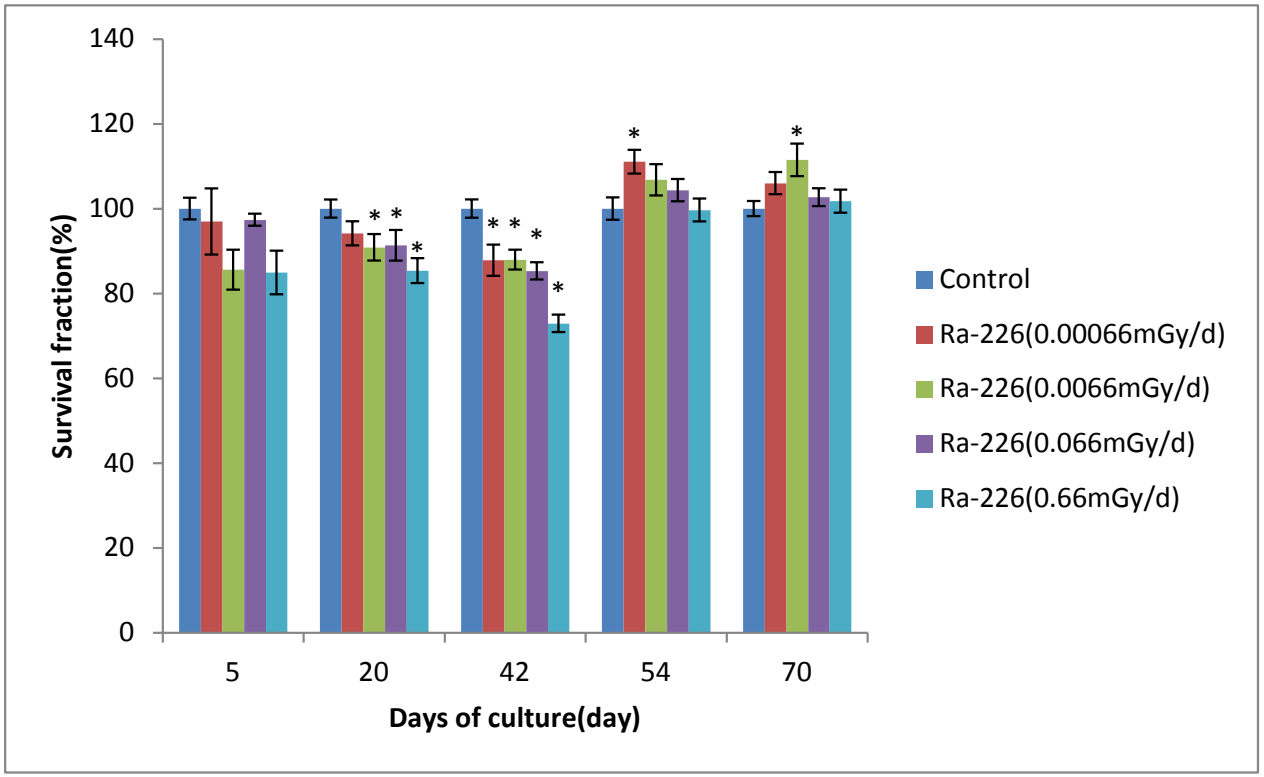


Fig 6 The survival fractions of HaCat cells cultured in medium with or without Ra-226, (n=9). Error bars represent SEM, n=9. Analysis was performed using two-way Analysis of Variance (ANOVA) method, and Post-hoc testing was performed with Fisher's least significant difference (LSD) test. A significant change when compared to the respective sample in Control group is represented by * ($p<0.05$).

Acute x-ray study with salmonids

- Fish exposed at early life stages to a single 0.5Gy x-ray and maintained at Alma hatchery
- F0 and F1 stages showed effects on proteome, stress signaling and biochemical indices but no impacts on growth or reproduction
- F2 assays just completed – NO IMPACTS AT ALL

Irradiation of rainbow trout at early life stages results in legacy effects in adults.

Mothersill C, **Smith** RW, Saroya R, Denbeigh J, Rowe B, Banevicius L, Timmins R, Moccia R, Seymour CB.

Int J Radiat Biol. 2010 Oct;86(10):817-28.

Smith RW, Seymour CB, Moccia R and Mothersill C, Transgeneration effects in F1 and F2 salmonids exposed at early life stages in F0 (just accepted)

Molecular genetic markers of radiation exposure

Why are they important

- Can be measured at the population level
- Can give information about population drift due to polymorphisms
- Can provide a picture of multiple changes in a population
- Are well worked out for humans and some model organisms

Individual to ecosystem

- Polymorphism is common in nature; it is related to biodiversity, genetic variation and adaptation; it usually functions to retain variety of form in a population living in a varied environment. It is heritable and is modified by natural selection

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Reflections Article

Genome-based, mechanism-driven computational modeling of risks of ionizing radiation: The next frontier in genetic risk estimation?☆,☆☆

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ABSTRACT

Research activity in the field of estimation of genetic risks of ionizing radiation to human populations started in the late 1940s and now appears to be passing through a plateau phase. This paper provides a background to the concepts, findings and methods of risk estimation that guided the field through the period of its growth to the beginning of the 21st century. It draws attention to several key facts: (a) thus far, genetic risk estimates have been made indirectly using mutation data collected in mouse radiation studies; (b) important uncertainties and unsolved problems remain, one notable example being that we still do not know the sensitivity of human female germ cells to radiation-induced mutations; and (c) the concept that dominated the field thus far, namely, that radiation exposures to germ cells can result in single gene diseases in the descendants of those exposed has been replaced by the concept that radiation exposure can cause DNA deletions, often involving more than one gene. Genetic risk estimation now encompasses work devoted to studies on DNA deletions induced in human germ cells, their expected frequencies, and phenotypes and associated clinical consequences in the progeny. We argue that the time is ripe to embark on a human genome-based, mechanism-driven, computational modeling of genetic risks of ionizing radiation, and we present a provisional framework for catalyzing research in the field in the 21st century.

Summary/Discussion

- New concepts need consideration due to paradigm shift in radiobiology
- Predicting low dose (rate) effects need new approaches involving multiple stressor approaches
- We can import good markers from human radiobiology especially system radiobiology which translates well to ecosystem radiobiology


Questions?