

Integrating Basic Biology and Epidemiology: Closing the Gap for Risk Assessment

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The Issue

- **Current attempts to estimate cancer and noncancer risks from radiation exposures at low doses (<100mGy) and low dose rates (<5mGy per hour) have resulted in significant uncertainties.**
- **A major component of these uncertainties is a consequence of an almost complete reliance on human epidemiology data obtained at relatively high doses for estimating effects at low doses and dose rates.**
- **The human data are clearly very important in risk assessment but their limitations have to be overcome.**
- **Enhancement in risk estimates cannot be achieved solely by designing and conducting larger and more directed epidemiology studies.**

A Possible Solution

- **A greater use has to be made of basic biology data from animal models and in vitro systems together with enhanced computational approaches to improve the quantitation of adverse health effects at low doses and dose rates.**
- **Some data of the types needed are already available from some 60 years of extensive research. Others will be available from studies that are underway and from future studies that are already feasible.**
- **A valuable review in this regard is that of Boss et al., Radiat Res 181, 561-577, 2014 (Linking the history of radiation biology to the hallmarks of cancer).**
- **An approach of this general type has been used in risk assessment for environmental chemicals for which epidemiology data are nearly always absent.**

Definitions (I)

- An “**adverse outcome pathway**” is an analytical construct that describes a sequential chain of causally linked key events at different levels of biological organization that lead to an adverse health effect.
- A “**key event**” is an empirically observable precursor step that is itself a necessary element of an adverse outcome pathway or is a biologically based marker for such an element.

Definitions (II)

When evaluating biological endpoints for use in risk assessment it is useful to differentiate between biomarkers of exposure, biomarkers of effect and bioindicators of cancer or noncancer effects.

Biomarkers of exposure and early effect include : DNA adducts mutations in reporter genes, mutations in genes not known to be related to cancer, chromosome alterations in non-target genes. These can be used to inform the shape of the dose response for an adverse health outcome.

Bioindicators are alterations that are specifically related to the development of an apical endpoint and include: mutations in cancer-related genes or chromosome translocations associated with specific cancers when identified in the target tissue. These bioindicators can be used to inform the dose response for an apical endpoint in a qualitative and quantitative manner.

Bioindicators are thus the key events along an adverse outcome pathway and are considered the most informative biological outcome in a risk assessment framework.

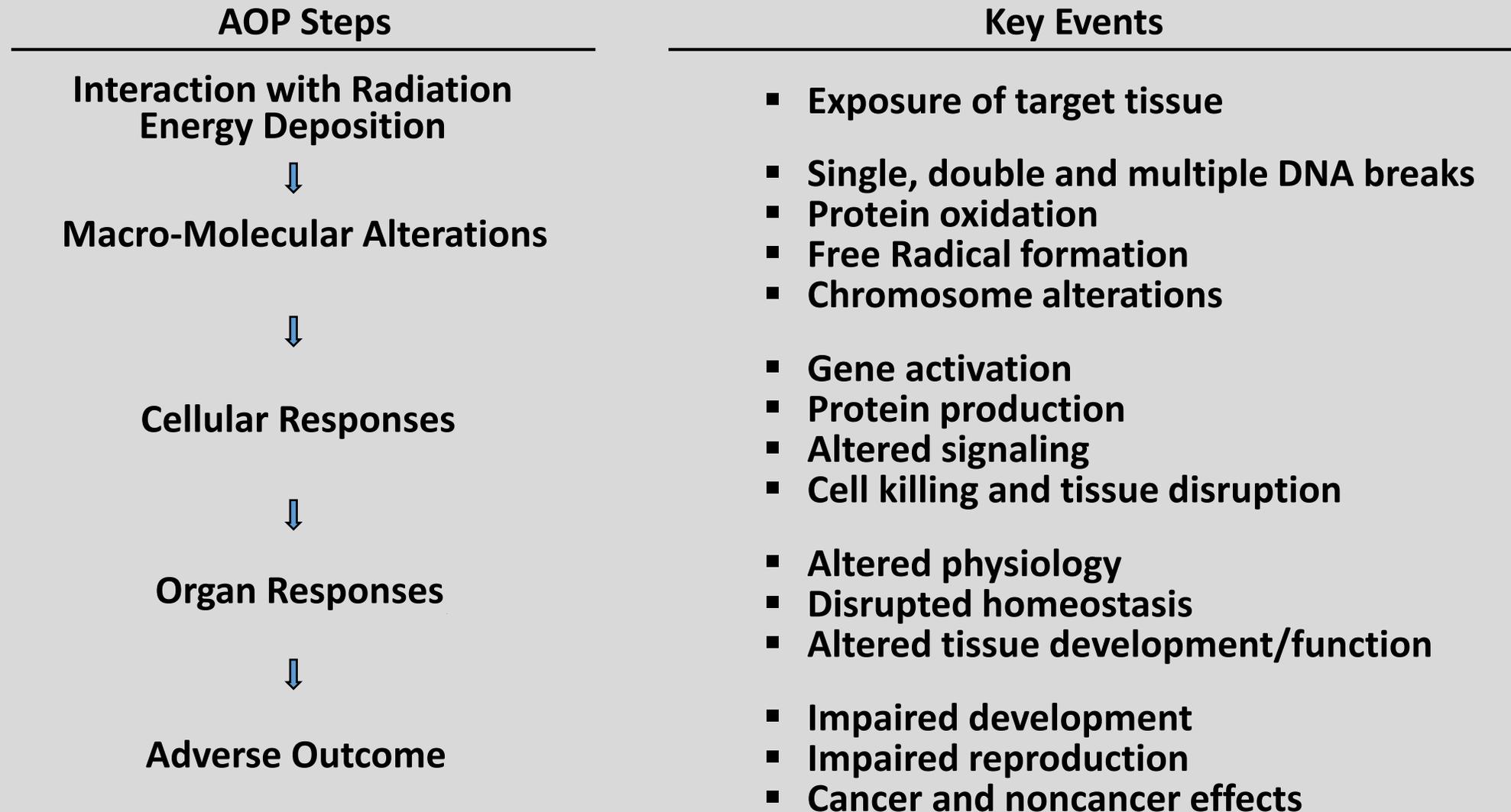
Biologically-Based Dose-Response (BBDR) Models

BBDR models combine the use of epidemiology, laboratory animal studies and cellular and molecular data in order to parameterize the model. The selection of parameters can be guided by a knowledge of the key events that lead to cancer development (adverse outcome pathway) in response to radiation.

The challenge in simple terms is to:

- 1. Understand a sufficient amount of the relevant biology**
- 2. Acquire enough knowledge to parameterize the model**
- 3. Develop the computational model**

Schematic representation of an adverse outcome pathway (AOP) for ionizing radiation-induced cancer and non-cancer diseases showing each step along the proposed pathway and the linked key events.



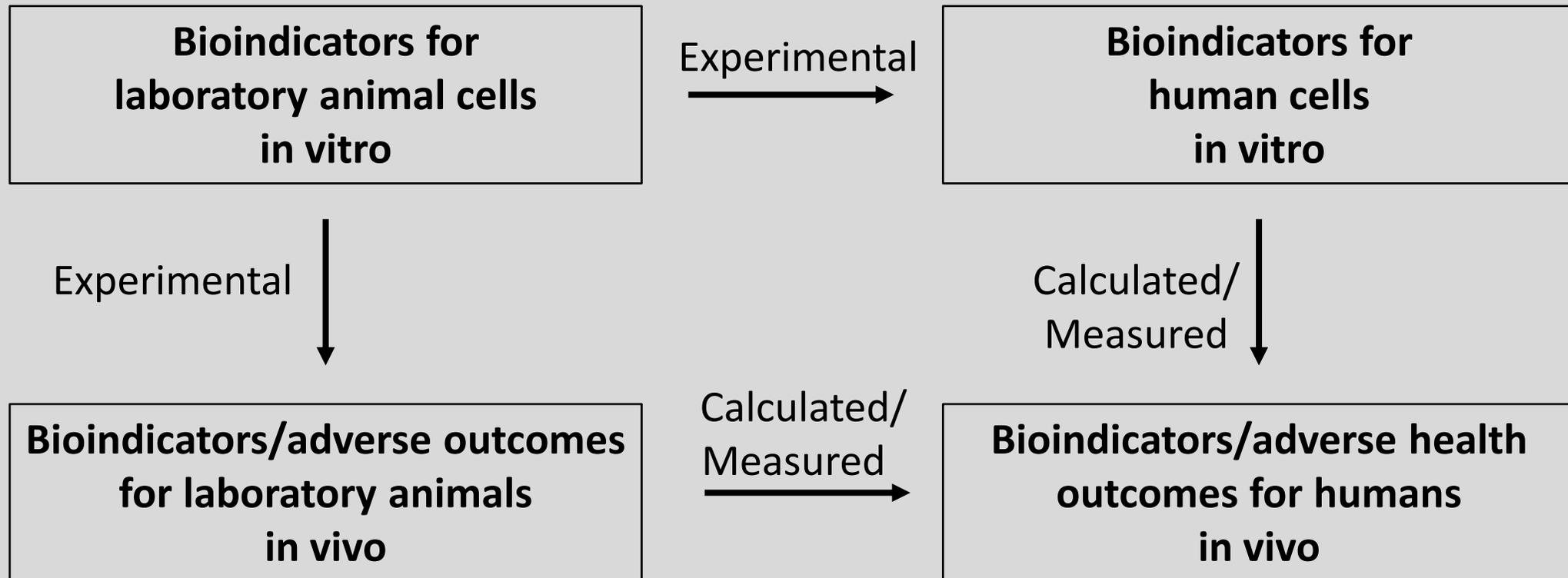
Key questions for testing AOP confidence

- 1. How well characterized is the AOP?**
- 2. How well are the initiating and other key events causally linked to the outcome?**
- 3. What are the limitations in the evidence in support of the AOP?**
- 4. Is the AOP specific to certain tissues, life stages or age classes?**
- 5. Are the initiating and key events expected to be conserved across taxa?**

Research Program

- The need is for the conduct of targeted research aimed at enhancing the risk assessment process at low doses and low dose rates. To do this the approach will be to identify and evaluate informative bioindicators of an apical response (cancer or noncancer) and use these to set parameters for a BBDR model. Based on our current knowledge, this is a viable approach although not a short term venture.
- These research activities have to be viewed in the context of ongoing and proposed epidemiology studies. Any viable approach has to be an integration of the biology and the epidemiology.

A parallelogram approach for utilizing laboratory animal and in vitro cell data to estimate human cancer and non-cancer risks for ionizing radiation



What Is Available?

- It is important to note that this is not “pie in the sky”; significant advances using this general approach have been made in the arena of environmental chemicals.
- For example, Adverse Outcome Pathways: From Research to Regulation (<http://ntp.niehs.nih.gov/go/729593>)
- For key events, the knowledge of the molecular basis for cancer and, to a lesser extent, for noncancer diseases is increasing very rapidly. New techniques such as ultra high speed sequencing are fueling this.
(Note Hanahan and Weinberg’s “Hallmarks of Cancer”)
- Predictive biologically-based models have been developed (e.g., Moolgavkar et al., 1979,1981; Little, 2010; Shuryak et al., 2010; Luebeck et al., 2013) and are becoming more relevant to the state of knowledge.
- Recent computational advances make linking molecular/cellular events to adverse outcomes much more readily feasible.

What is Needed?

- **Increased knowledge of key events for radiation-induced adverse health outcomes. Are there “radiation signatures” of response?**
- **Development or enhancement of adverse outcome pathways.**
- **Identification and evaluation of key events/bioindicators.**
- **Development of new and improved BBDR models.**
- **Epidemiology studies directed to low dose and low dose-rate exposures.**