APPROACHES FOR INTEGRATING INFORMATION FROM RADIATION BIOLOGY AND EPIDEMIOLOGY TO ENHANCE LOW-DOSE HEALTH RISK

Report of NCRP SC1-26

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Background for Report

Issue: The health risks at low radiation doses (<100mGy) and dose rates (5mGy/hr) remain quite uncertain and even with high quality epidemiology studies these uncertainties cannot be adequately addressed. Reliance on LNT is hotly debated even though it remains the best approach based on the available data.

Approach: There are and can be available biological data that might be able to enhance the estimation of risk at low doses and dose rates if these can inform the underlying mechanism of radiation-induced health effects (for this Report cancer and circulatory disease). Thus, the integration of epidemiology data and informative radiation biology data in biologically-based dose-response (BBDR) models is deemed to be a viable approach.

Background

- **NCRP Report No. 171, *Uncertainties in the Estimation of Radiation Risks and Probability of Causation* (NCRP, 2012)**
- **NCRP Commentary No. 24, 275 *Health Effects of Low Doses of Radiation: Perspectives on Integrating Radiation Biology and Epidemiology* (NCRP. 2015)**
- **NCRP Commentary No. 27, *Implications of Recent Epidemiologic Studies for the Linear-Nonthreshold Model and Radiation Protection* (NCRP, 295 2018)**
- **These all included proposals that integration of epidemiology and radiation biology was a viable approach**

Framework

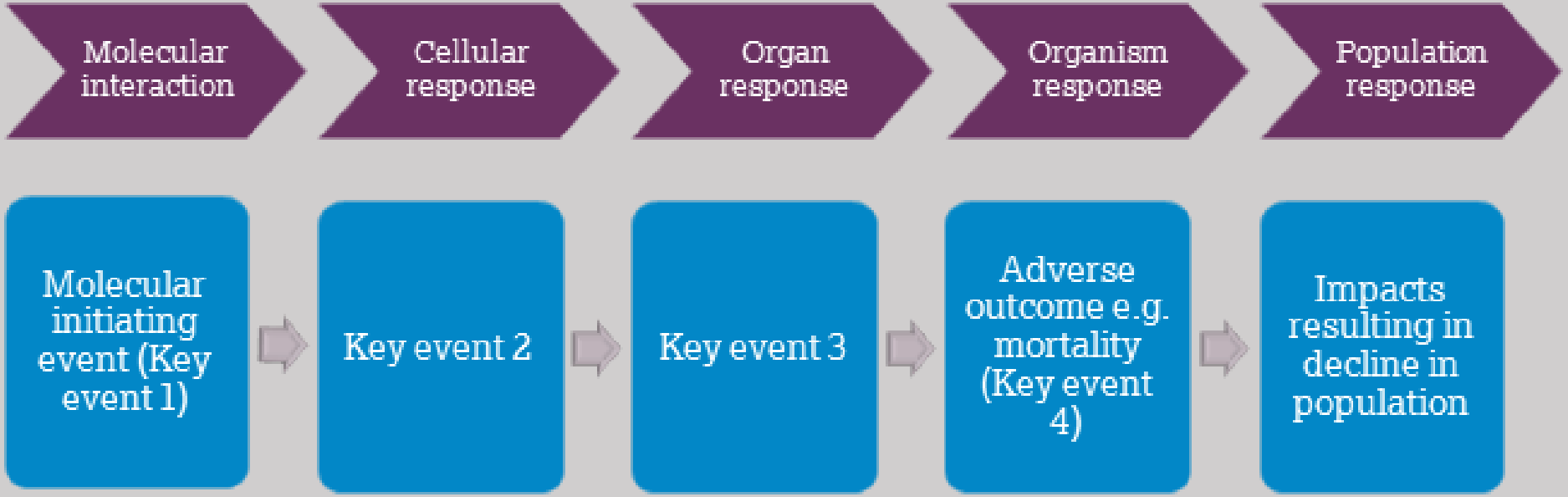
- **The proposed approach built upon that used in the field of risk assessment for environmental chemicals, namely to develop adverse outcome pathways for radiation-induced cancer and noncancer effects (specifically circulatory disease) and to identify the key events along such pathways.**
- **Key events are envisaged to be used as parameters in biologically based dose-response (BBDR) models for estimating risks at low doses and low dose rates. Simple and sophisticated BBDR models have been developed over a number of years but as knowledge of the etiology of adverse health outcomes has been greatly enhanced in the past few years, more and more realistic and predictive models have and can be developed.**

Adverse Outcome Pathways and Key Events - Definitions

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 defined as "an empirically observable precursor step that is itself a necessary element of the mode of action (*adverse outcome pathway)* or is a biologically-based marker for such an element".

Generalized Adverse Outcome Pathway



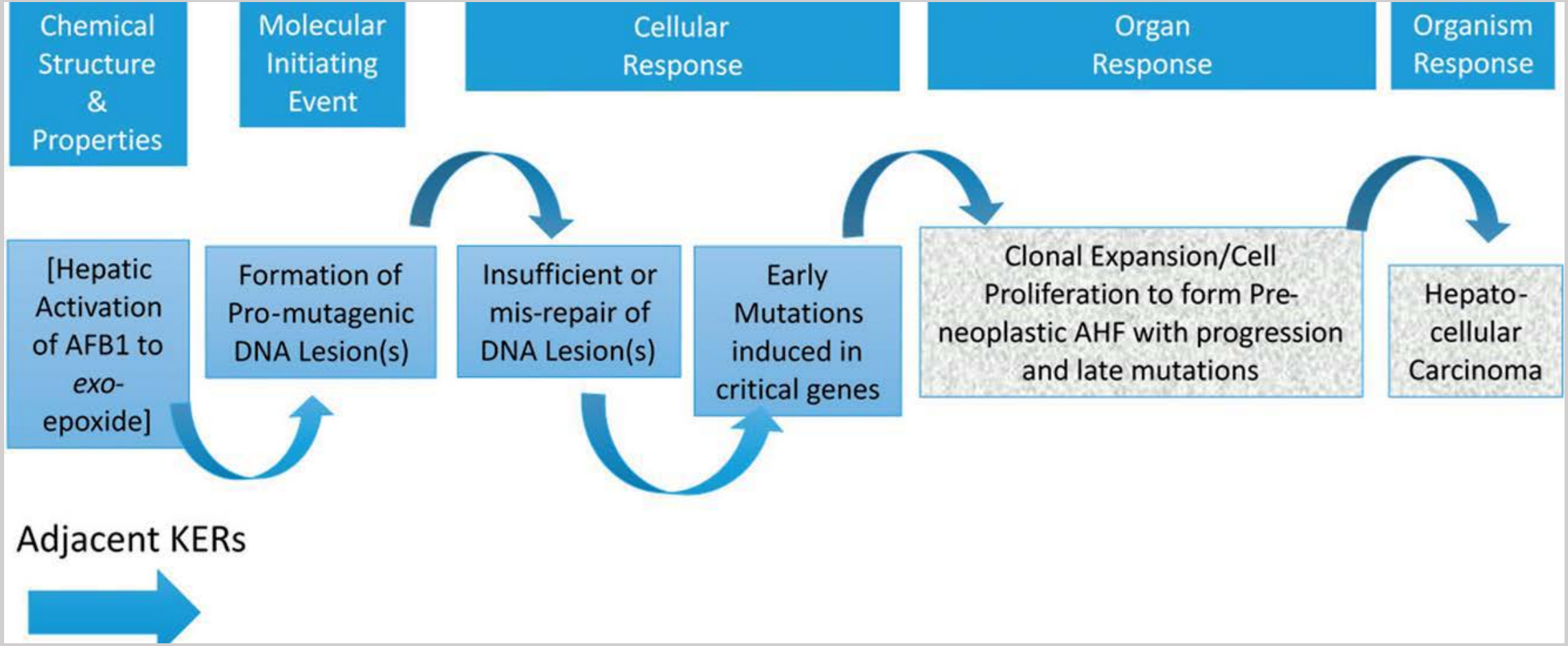


Fig. 6.1. Adjacent key event relationships (KERs) for the adverse outcome pathway on mutagenic mode of action for hepatocellular carcinoma (HCC) induction by aflatoxin B1 (AFB1): formation of pro-mutagenic DNA adducts leads to HCC (Moore et al., 2018).

Examples of Key Events Along AOPs for Radiation-induced Adverse Health Effects

AOP Steps	Key Events
Interaction with Radiation Energy Deposition	▪ Exposure of Target Tissue
⇩	
Macro-Molecular Alterations	▪ Single, double and multiple DNA breaks ▪ Base modification ▪ Protein Oxidation ▪ Free Radical Formation ▪ Chromosome Alterations ▪ Gene mutations
⇩	
Cellular Responses	▪ Gene Activation ▪ Protein Production ▪ Altered Signaling ▪ Cell killing and Tissue Disruption
⇩	
Organ Responses	▪ Altered Physiology ▪ Disrupted Homeostasis ▪ Altered Tissue Development/Function
⇩	
Adverse Outcome	▪ Impaired Development ▪ Impaired Reproduction ▪ Cancer and Non-cancer Effects

General Outline

- **What we know – radiation epidemiology; underlying biology of cancer and circulatory disease; radiation responses; and BBDR models of radiation-induced cancer and in general**
- **What we need to know – selected examples of adverse outcome pathways for cancer and circulatory disease in response to radiation; key events associated with these pathways; general BBDR models for cancer and circulatory disease**
- **Research to obtain the required data and models**

Epidemiology

- **NCRP recently reviewed the major radiation epidemiology studies and the impact they had on cancer dose-response curves and LNT in particular (NCRP Commentary No. 27).**
- **Thus, Report SC1-26 concentrated on review of those major studies for cancer and circulatory disease that had biological samples associated with them that could be used in mechanistic studies. This would be part of integrating radiation biology data and epidemiology.**
- **Report provides a list of all the known available human samples from irradiated human groups/populations.**

Potential for Integration

The most viable approach is to identify and quantitate informative bioindicators of cancer and circulatory disease as parameters in appropriate models. A secondary approach is to use biomarkers of response.

- A biomarker is a biological phenotype (e.g. chromosome alteration, DNA adduct, gene expression change, specific metabolite) that can be used to indicate a response to an exposure at the cell or tissue level. In this regard, it is generally a measure of the potential for development of an adverse outcome such as cancer (e.g. a predictor of exposure level).
- A bioindicator is defined as a cellular alteration that is on a critical pathway to the disease endpoint itself (i.e. necessary, but not by itself sufficient for the endpoint), such as a specific mutation in a target cell that is associated with tumor formation.

Radiation-Induced Biological Effects Related to Cancer and Circulatory Disease

This topic area considers the mechanisms and pathways known to be involved in the pathogenesis of the broad classes of disease identified to be important for ionizing radiation risk assessment. There are two main classes of disease that are considered:

- **cancers, including leukemia; and**
- **circulatory disease (as a non-cancer disease)**

The current state of knowledge on the pathogenesis of cancer and circulatory disease is extensive yet remains incomplete. This is due to the complexity of these conditions, and the diversity of the human population. These two major classes of disease are considered separately, firstly in terms of the mechanisms and pathways driving the diseases in general and secondly in terms of those mechanisms and pathways known or reasonably suspected to be influenced by radiation exposure. Through this understanding of the radiation affected mechanisms and pathways, suitable bioindicators may be identified that will be of use in directing research efforts to gather appropriate quantitative data to integrate into mechanistic models.

Biomarkers and Bioindicators

- **The Report discusses known and possible bioindicators and biomarkers of cancers and circulatory disease and the types of endpoints that might serve as bioindicators of these diseases.**
- **To make this a more viable approach, specific research is discussed in a later section that is designed around the identification of specific bioindicators/key events along potential AOPs**

Biologically Based Dose-Response (BBDR) Models

- **The Report assesses biomathematical models of chronic disease, especially those for cancer and circulatory disease. First, general material outlining the overall goals of biomathematical models is presented, followed by discussion of modeling considerations, particularly application of specific models using human, animal and/or cell data for cancer and circulatory disease.**
- **Models of cancer development and their differences from descriptive models are discussed. A number of BBDR models and their application to various human and animal data sets are presented.**
- **The discussion follows the historical path from early rather simple BBDR models such as multistage models without clonal expansion and the two-stage clonal expansion model, towards more recent BBDR models that involve multiple pathways.**

Generalized MVK Model

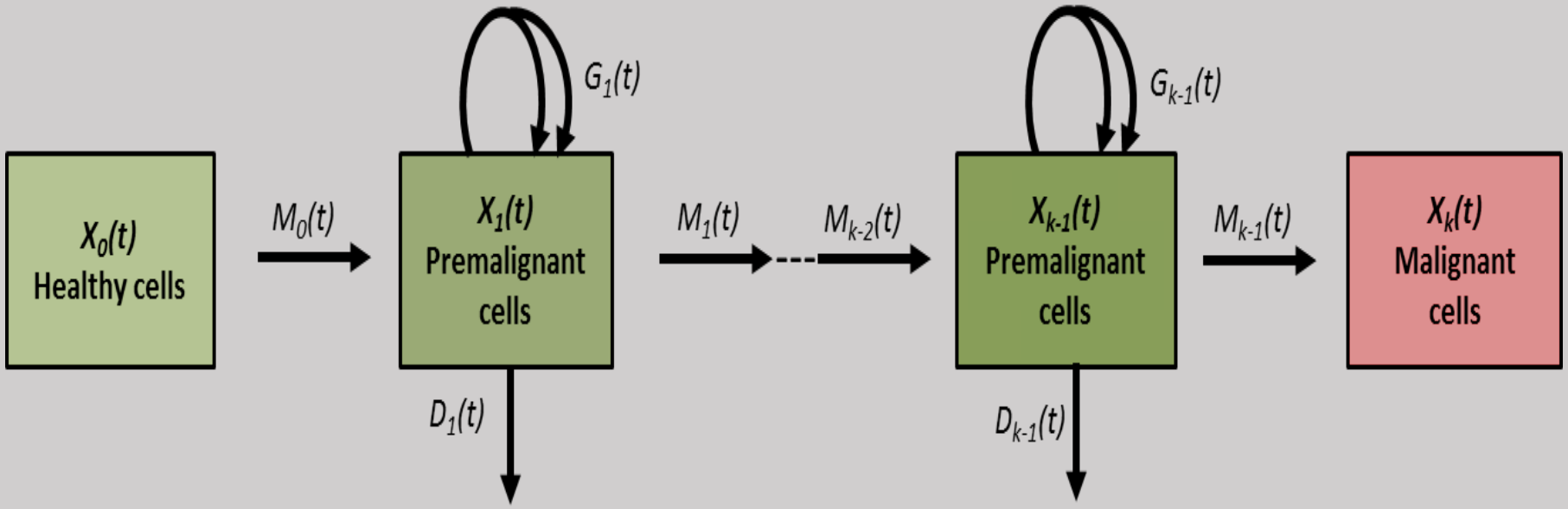


Fig. 5.4. Schematic diagram of the generalized MVK model (Little, 1995). The $M_i(t)$ are the intercompartment rate-limiting mutation rates, $G_i(t)$ and $D_i(t)$ are the intracompartmental growth and death/apoptosis rates, respectively, with $X_i(t)$ denoting the number of cells in compartment number *i* at age *t*, so that $X_0(t)$ denotes the number of healthy, untransformed stem cells at that age. The subscript *k* in the figure refers to the total number of stages.

Multiple Pathway Models of Cancer

- **Multiple pathway models are intrinsically flexible, allow consideration of various biological phenomena (*e.g.*, genomic instability, intercellular communication and nontargeted effects of ionizing radiation), and can also address the individual molecular background of a certain cancer type if needed. In certain cases they may allow predictions that can be validated against experimental data.**
- **Although a number of other models are also discussed (e.g., evolutionary models), multiple pathway models are considered, despite their shortcomings (*e.g.*, the fact that different models might explain the available data using different mechanistic assumptions), as the most promising conceptual approach for the development of a general model framework to be applied for modeling the complex process of carcinogenesis in various tissues.**

Circulatory Disease Models

Circulatory disease models are less well developed than those that have been constructed to model cancer. A number of candidate models of atherosclerosis are considered. At this time a generalized model cannot readily be described.

Proposed Generalized Model Framework of Cancer and Circulatory Disease

- **The Report proposes that the generalized multistage clonal expansion model developed by Little et al. can be used for modeling cancer(Little MP et al. Systems biological and mechanistic modelling of radiation-induced cancer. *Radiat Environ Biophys* 47(1): 39-47).**
- **This is a very general and flexible model, special cases of which have been fitted to a large number of radiation-induced and nonradiation-induced cancer data sets.**
- **This model can very naturally also take account of a population, including groups with elevated cancer risks because of heritable gene inactivation (*e.g.*, retinoblastoma and Li-Fraumeni syndrome).**
- **The Report addresses the issue of parameter identification, which is often a problem with such highly parameterized models.**

Bioindicators/Key Events as Parameters for Generalized BBDR Model

- For the identification of informative bioindicators of adverse health outcomes that can be considered as usable parameters for generalized cancer BBDR models, it is proposed to incorporate an adverse outcome pathway/key event framework into the generalized models. It is necessary to describe such pathways for specific radiation-induced cancers (and subsequently, circulatory disease) as a first step and then to additionally identify key events along such pathways. This is a major undertaking but feasible as discussed in the Section on Research Needs.

Research Needs and Experimental Approaches (I)

- **The overarching theme of this NCRP Report is the integration of epidemiology and radiation biology to enhance the estimation of adverse health outcomes at low doses and low dose rates of radiation. Such integration will lead to the development of a form of BBDR model that will specifically include informative parameters at low doses and low dose rates.**
- **The framework that is proposed for identifying such parameters centers on the concept of adverse outcome pathways and their associated key events. Currently, relatively few such adverse outcome pathways have been described for specific exposure scenarios with almost none for radiation. Thus, an essential need is to establish a research initiative to identify adverse outcome pathways and key events for radiation-induced cancers and as feasible for noncancer outcomes.**

Research Needs and Experimental Approaches (II)

- The approaches described in detail in the Report highlight the advances in technology and experimental animal and cellular systems that can hugely advance this effort. While the task is expansive, the feasibility of success is high. There are comprehensive discussions of additional data needs and additional model development and testing needs that identify approaches that are currently available or are anticipated to become available in the near future.
- A series of specific research needs and experimental approaches are presented as examples of what can be done now or what is likely to be achievable in the near future.

Examples of Resources for Identifying AOPs and Key Events

- Li J et al. Identification of biomarker genes in individual tumor samples (2019) Frontiers in Genetics, Volume 10: Article 1236

- Alexandrov LB et al. (PCAWG Consortium) The repertoire of mutational signatures in human cancer (2020) Nature 578: 94-101

- Collier O et al. LOTUS: A single- and multitask machine learning algorithm for the prediction of cancer driver genes (2019) PLoS Comput Biol eCollection 2019 Sep.