Human Health Research Program (2006-2013)

OVERVIEW OF LTG-1: USE OF MECHANISTIC DATA IN RISK ASSESSMENT

R. Julian Preston (NHEERL)
LTG Lead

BOSC Review, 2009

Overall Goal

ORD's research plan for LTG-1 is defined in the Human Health Research Plan (2006-2013) as addressing the requirement for risk assessors and risk managers to use ORD's methods, models or data to address uncertainty in risk assessment using mechanistic (or mode of action) information.

Research Questions

The research in LTG-1 is guided by a set of key research questions:

- **What methods and models are needed to identify modes or mechanisms of action that can be used for risk assessment?**
- **How can knowledge of toxicity pathways inform the development of PK and PD models for risk assessment?**
- **How can knowledge of toxicity pathways (or mode of action) be used to reduce uncertainty in extrapolation in risk assessment, including**
  - **Extrapolation from high to low dose?**
  - **Extrapolation from laboratory animals to humans?**
  - **Extrapolation from *in vitro* data to *in vivo* exposures?**
  - **Harmonization of cancer and non-cancer risk assessments?**

Strategy for LTG-1 Research Plan

- **Develop a comprehensive research implementation plan that consists of a set of research projects that are designed to investigate the key events in the MOA for adverse health outcomes. Specific chemicals are necessarily used to address the research goal but the questions being asked have implications across a broad range of chemicals and chemical classes.**

Definitions

Mode of Action (MOA) is defined as "a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation."

A ***Key Event*** is an "empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element".

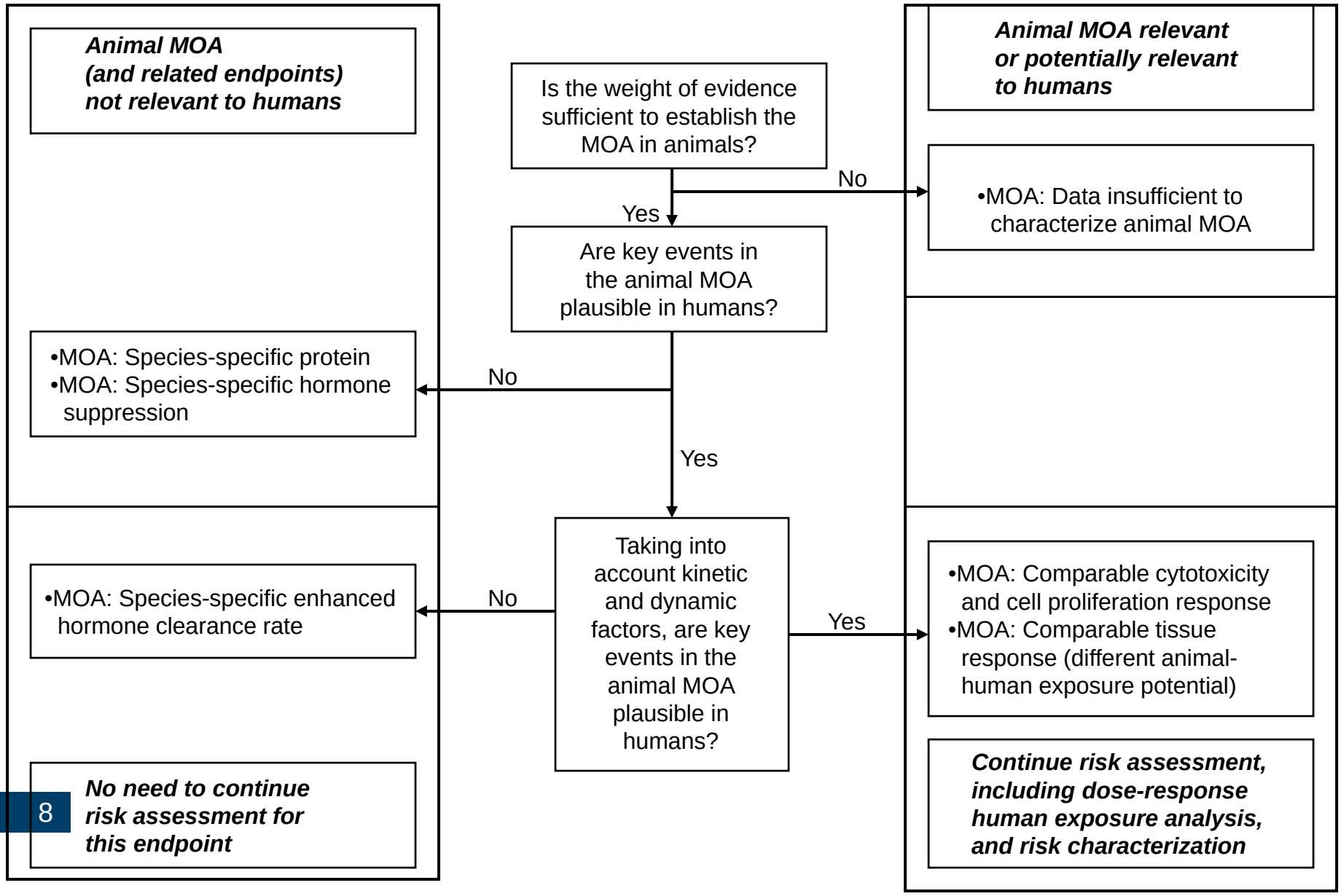
A ***biomarker*** is considered to be a surrogate marker of exposure or an early biological marker of effect (e.g., mutations in reporter genes, total chromosome alterations). In contrast, a biological marker of effect that is itself a key event along the pathway from a normal cell to a transformed one is described as a ***bioindicator*** (e.g., mutation in a critical gene for cancer, cancer-specific chromosome translocation).

Framework for Risk Assessments

A framework has been developed by U.S. EPA, ILSI and IPCS that is proposed for use for the conduct of both cancer and non-cancer risk assessments. It is based on an animal MOA and Human Relevance Framework (HRF). The use of an animal MOA is necessitated by (a) the current lack of pertinent human epidemiological data and (b) the availability of much of the mechanistic data being from animal models.

Animal MOA and HRF

- **Key events are identified that support a specific MOA in animals for a cancer or non-cancer endpoint. Using these a MOA is developed for a particular chemical in an animal model. The human relevance of this MOA is then established using the HRF. Decisions on the necessity for a quantitative risk assessment are made on the basis of the use of the HRF.**


Is the weight of evidence sufficient to establish the MOA in animals?
No
•MOA: Data insufficient to characterize animal MOA
Yes
Are key events in the animal MOA plausible in humans?
No
•MOA: Species-specific protein
•MOA: Species-specific hormone suppression
Yes
Taking into account kinetic and dynamic factors, are key events in the animal MOA plausible in humans?
No
•MOA: Species-specific enhanced hormone clearance rate
Yes
•MOA: Comparable cytotoxicity and cell proliferation response
•MOA: Comparable tissue response (different animal-human exposure potential)
Animal MOA relevant or potentially relevant to humans
Animal MOA (and related endpoints) not relevant to humans
No need to continue risk assessment for this endpoint
Continue risk assessment, including dose-response human exposure analysis, and risk characterization

Key Input Data for Risk Assessment Framework

- **Key events for MOA – mechanistic data in mammalian and human cells, animal models and humans**
- **MOA development from key events and models (toxicity pathways)**
- **Toxicity data from animal models (targeted testing)**
- **Human epidemiological data whenever possible for HRF**
- **All these data inputs can be used in a quantitative risk assessment if this is required**

Relationship to Other LTGs in HHRP

The development of bioindicators of adverse health outcomes that will be a product of LTG-1 mechanism-based research are a cornerstone to:

- **A mechanistic approach to the conduct of cumulative risk assessments (LTG-2)**
- **A better understanding of the basis for individual and population susceptibilities and sensitivities (LTG-3)**
- **Assessment of the outcomes of risk management decisions (LTG-4).**

LTG1 Project Overview

The projects that constitute LTG1 are grouped into 5 Themes that address different aspects of the development of models and approaches for incorporating mechanistic data into risk assessments.

Theme 1: Determine utility of emerging technologies in risk assessment

Theme 2: Develop MOA data for reproductive and developmental risk

Theme 3: Identify PK/PD issues underlying uncertainties for extrapolation

Theme 4: Identify the roles for oxidative stress in cancer and noncancer risk assessments

Theme 5: Establish systems-based models for use in risk assessments

Theme 1: Determine utility of emerging technologies in risk assessment

LTG1-01 Application of Toxico-omics to Enhancing Risk Assessments – MOA of Conazoles

LTG1-02 Use of Toxico-genomics to Discriminate Conazoles and Related chemicals from Phenobarbital for Human Relevancy Determinations in Cancer Risk Assessments.

Theme 2: Develop MOA data for reproductive and developmental risk

LTG1-03 Cellular and Molecular Modes Responsible for Induction of Birth Defects

LTG1-04 Linking an in vivo Pregnancy Loss Model to an in vitro Placental Cell System to Explore the Mode of Action of Disinfection Byproducts

LTG1-05 The Effects of Environmental Chemicals on Neuroendocrine Function: Mode and Mechanism for Adverse Outcomes

Theme 3: Identify PK/PD issues underlying uncertainties for extrapolation

LTG1-06 How Does ORD Research on MOA Contribute to the Human Health Risk Assessment for PBDE Mixtures?

LTG1-07 Arsenical Metabolism and Dosimetry: The Bridge Between Arsenic Exposure and Health Effects for Risk Assessments.

Arsenic Research in LTG-1

- **The project that was originally designed to support the cancer risk at low concentrations of arsenic based upon the operation of multiple MOAs has been reevaluated in light of new information to concentrate on the dosimetric aspects of arsenic toxicity and carcinogenicity. In discussions with the Agency's Office of Water and an external advisory panel, it became clear that a BBDR would not enhance the assessment of low dose cancer risk for the purposes of regulation. What was really needed was a much clearer understanding of the tissue dosimetry for inorganic arsenic and its methylated metabolites. Thus, the project has turned its focus to PBPK modeling for estimating effective doses to target tissues.**

Theme 4: Identify the roles for oxidative stress in cancer and noncancer risk assessments

LTG1 – 09 Progress Toward the Use of Oxidative Stress as a Broadly Applicable Key Event in Environmental Toxicity

LTG1-10 Future Application of Oxidative and Other Stress Pathways to Mode of Action Studies

Theme 5: Establish systems-based models for use in risk assessments

LTG1-11 Systems Biology and Toxicity Testing in the Twenty-first Century

LTG1-12 Development of Virtual Tissue Models

LTG1-13 Development and Use of Biologically-Based Dose Response (BBDR) Models

LTG1-14 Constructing a Biologically-based Dose Response (BBDR) Model to Refine Risk Assessment Approaches to Respiratory Effects from Inhaled Reactive Gases: Chlorine

Conclusions

- **We are firmly of the view that this current LTG-1 research program (represented by LTG1 Abstracts 1-10) meets its goal of addressing the requirement for risk assessors and risk managers to use ORD's methods, models or data to address uncertainty in risk assessment using mechanistic (or mode of action) information.**
- **As we develop our plans for the future, with this same goal in mind, we are initiating an integrated toxicology- systems approach to respond to the challenges presented by the Futures of Toxicity Testing Strategic Plan and the NAS Report on the Future of Toxicity Testing (represented by LTG 1 Abstracts 11-14). These approaches take full advantage of new whole genome assessments and their link to adverse outcomes in animal models and ultimately humans through the application of a MOA and human relevance framework.**