Components of the Dioxin Reassessment

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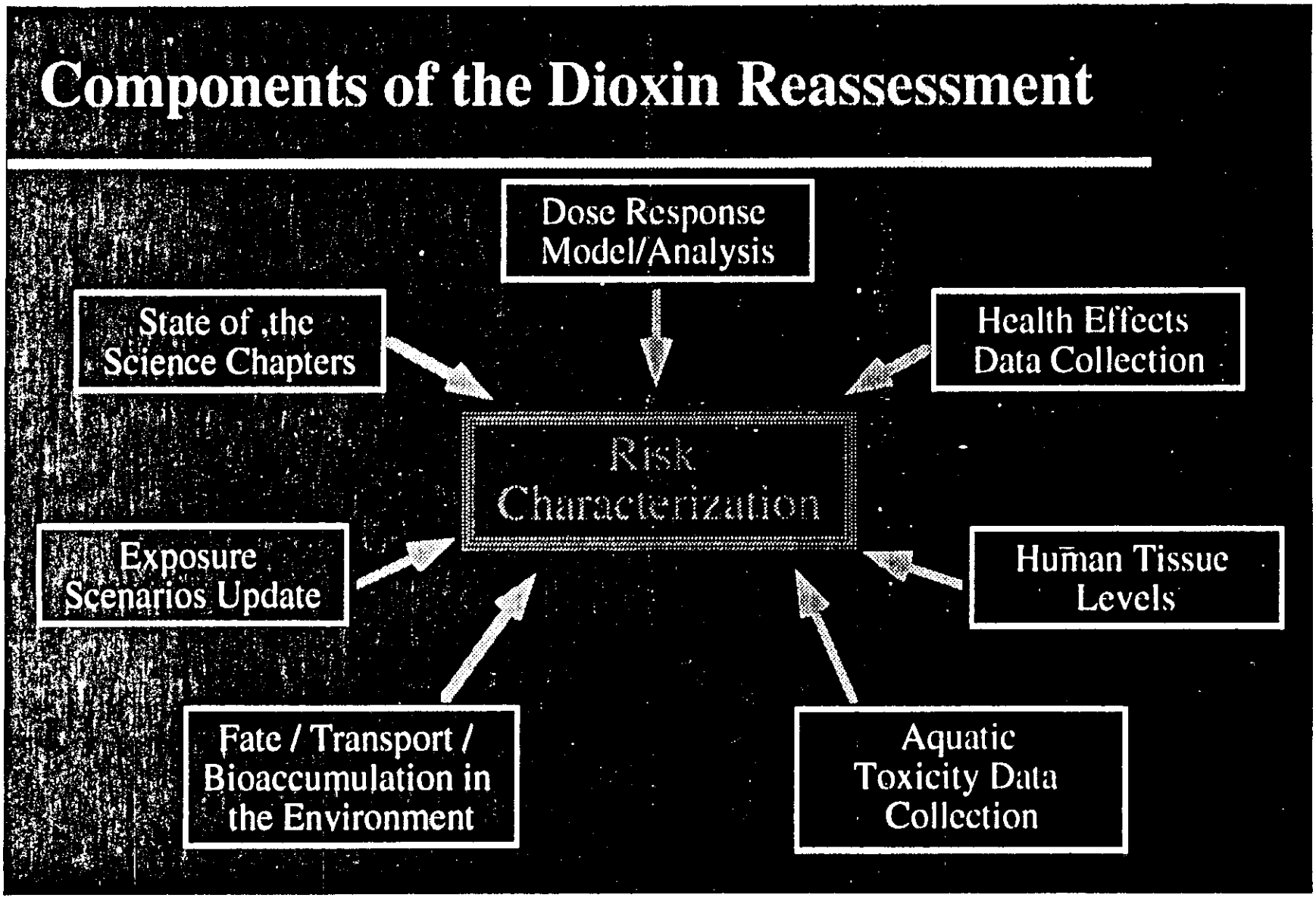
Components of the Dioxin Reassessment
Dose Response Model/Analysis
State of ,the Science Chapters
Health Effects Data Collection
Risk Characterization
Exposure Scenarios Update
Human Tissue Levels
Fate / Transport / Bioaccumulation in the Environment
Aquatic Toxicity Data Collection

Development of a "Strawman" Biologically-Based Dose Response Model for Dioxin

Approaches

- Evaluation of empirical data *(Top down)*
- Theoretical considerations based on mechanism(s) of-action *(Bottom up)*

Development of a "Strawman" Biologically-Based Dose Response Model for Dioxin

Key Personnel

- Dr. Michael Gallo and colleagues from the Robert Wood Johnson School of Medicine and Dentistry in New Jersey
- Dr. George Lucier and colleagues from NIEHS
- EPA biostatisticians / modelers
- Other collaborators from Federal, industrial, academic sectors

Development of a "Strawman" Biologically-Based Dose Response Model for Dioxin

Outputs

- "Strawman" approach to evaluating dose response characteristics for various "dioxin-like" effects, from early biochemical and biological responses (adaptive) to frank toxicologic effects (adverse).
- Narrative chapter describing the model to feed into risk characterization.

State-of-the-Science Chapters

Chapter Title: Disposition and Pharmacokinetics

Primary Author: James Olson
Dept. Pharmacology & Therapeutics
SUNY, Buffalo

EPA Chapter Manager: Jerry Blancato
Environmental Monitoring Systems
Laboratory - Las Vegas

State-of-the-Science Chapters

- Chapter: Disposition and Pharmacokinetics
  - Focus:
    - Absorption / bioavailability following exposure
    - Distribution in the body
    - Metabolism and excretion
    - Development of physiologically based pharmacokinetic model
    - Pharmacokinetics in special populations

State-of-the-Science Chapters

Chapter Title: Mechanism(s) of Toxic Actions

Primary Author: James Whitlock, Jr.
Dept. of Pharmacology
Stanford Univ. School of Medicine

EPA Chapter Manager: William Farland
Office of Health & Environmental Assessment

State-of-the-Science Chapters

Chapter: Mechanism(s) of Toxic Actions

Focus:

- Receptor interactions
- Transfer to the cell nucleus
- DNA binding
- Impact on genetic activity

State-of-the-Science Chapters

Chapter Title:	Toxicology: Acute, Subchronic, Chronic
Primary Author:	Ulf G. Ahlborg Karolinska Institute Stockholm, Sweden
EPA Chapter Manager:	Debdas Mukergee Environmental Criteria and Assessment Office - Cincinnatti

State-of-the-Science Chapters

Chapter: Toxicology: Acute, Subchronic, Chronic

Focus:

- Signs / symptoms of toxicity
- Range of sensitivities - endpoints / species
- Special effects associated with dioxin toxicity

State-of-the-Science Chapters

Chapter Title: Toxicology: Immunotoxic Effects

Primary Author: Nancy Kerkvliet
College of Veterinary Medicine
Oregon State University

EPA Chapter Manager: Gary Burleson
Health Effects Research Laboratory
- RTP

State-of-the-Science Chapters

Chapter: Toxicology: Immunotoxic Effects

Focus:

- Recent developments in the field of dioxin immunotoxicity
- Indirect mechanisms of TCDD immunotoxicity
- Comparison across tissues / species
- Host resistance as an end point of evaluation

State-of-the-Science Chapters

Chapter Title: Toxicology: Reproductive / Developmental Effects

Primary Author: Richard Peterson
School of Pharmacy
University of Wisconsin

EPA Chapter Manager: Gary Kimmel
Human Health Assessment Group

State-of-the-Science Chapters

- Chapter: Toxicology: Reproductive / Developmental Effects
- Focus:
  - Male and female reproductive function / fertility
  - Overt embryo / fetal effects
  - Postnatal effects

State-of-the-Science Chapters

Chapter Title: Toxicology: Carcinogenicity

Primary Author: George Lucier
National Institute of Environmental
Health Sciences

EPA Chapter Manager: Charalingayya Hiremath
Human Health Assessment Group

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State-of-the-Science Chapters

Chapter: Toxicology: Carcinogenicity

Focus:

- Initiation / promotion assays
- Role of hormones, growth factors, etc.
- Cell proliferation

State-of-the-Science Chapters

Chapter Title: Toxicology: Epidemiology / Human Data

Primary Author: Charles Poole
Epidemiology Research Institute
Cambridge, Mass

EPA Chapter Manager: David Bayliss
Human Health Assessment Group

State-of-the-Science Chapters

Chapter: Toxicology: Epidemiology / Human Data

Focus;

- Recent studies evaluating carcinogenicity
- Literature review on non-cancer endpoints
- Human / animal comparison at high dose levels

External Review Draft - June, 1992

- Seven state-of-the-science chapters
- Dose - response chapter
- Draft risk characterization

Exposure Scenarios Document

Purpose:

- Describe procedures for estimating exposure to dioxin and related chemicals

Scope (1988 document):

- Sources - contaminated soil and incinerators
- Pathways -
  - Dust Inhalation
  - Vapor inhalation
  - Dermal contact with soil
  - Soil ingestion
  - Ingestion of beef and dairy products
  - fish ingestion
  - Water ingestion
  - Fruit and vegetable ingestion

Exposure Scenarios Document

General changes from the 1988 document:

- Addition of dioxin, furan, and PCB congeners
- Reevaluation of fish consumption
- Pharmacokinetics
- Expanded scenarios

Three Phase Process for Review of the Chapters and Dose-Response Model

Phase 1:

- Review of the state-of-the-science chapters; new dose-response model by peer review panel in June, 1992.
- Objective is to reach scientific consensus on:
  - Scientific integrity of the state-of-the-science chapters
  - Scientific validity of the model

Process for Review

Phase 2:

- Preparation of the risk characterization. July, 1992.

Objective:

- To ask Peer Panel to discuss and formulate the critical points to be carried into the risk characterization.
- To have the panel 'author' the risk characterization to help achieve consensus within the general scientific community.

Process for Review

Phase 2 - Continued . . .

- Risk characterization likely to contain 3 parts:
  - Characterization of the risk (qualitatively and quantitatively) for 2,3,7,8-TCDD and related dioxins and furans.
  - Characterization of the risk qualitatively for co-planar PCBs, and determination if enough data exist to characterize the risk quantitatively.
  - Combination of the two efforts above to characterize the risks qualitatively and quantitatively, as appropriate.

Process for Review

- Phase 3:
  - Review of the Health Effects Assessment and the Exposure Documents by the Science Advisory Board and the public. Fall, 1992.
    - The risk characterization, the state-of-the-science chapters, the chapter on the development of the model, and the exposure document will be brought to the SAB for review in the early Fall of 1992.
    - Comments from the public will be solicited at the same time.

Process for Review

Next Steps

- Receipt of SAB review and public comments.
- Rewriting of reports as appropriate.
- Review of revised reports by SAB.

Aim is to complete this entire process by the Fall of 1993.