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EPA's Scientific Reassessment
of Dioxin

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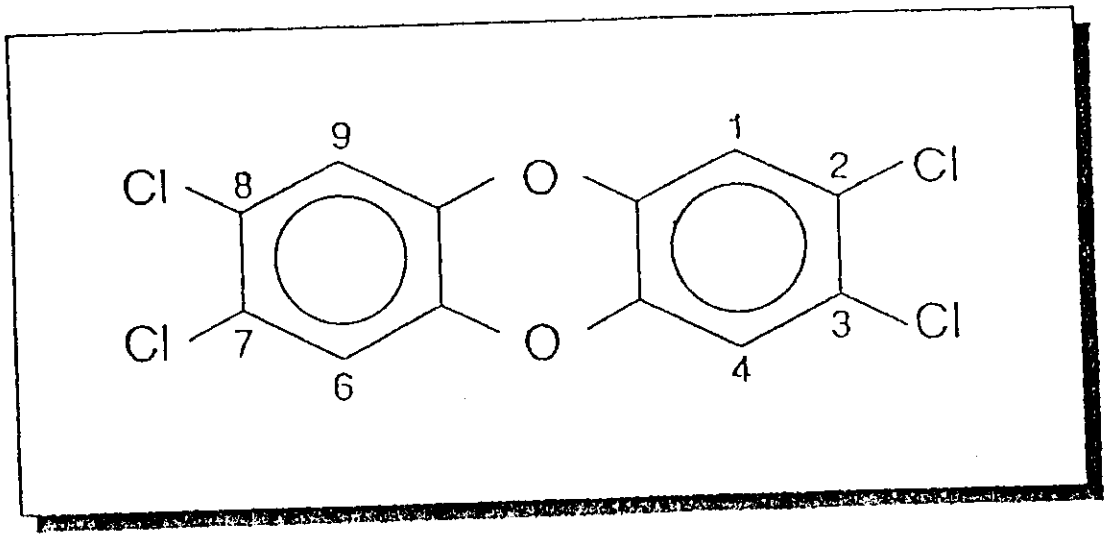
Office of Research & Development

EPA's Scientific Reassessment of Dioxin



A STATUS BRIEFING
FOR THE ADMINISTRATOR
Deputy

~~JANUARY 27~~, 1992
Feb 14

I will discuss.....

1. Background and history.
2. Where we are in the reassessment process.
3. ORD's interactions with the public on this project.
4. Some recent scientific results and conclusions.
5. Issues relevant to dioxin-like PCBs
6. Summary and overview.

1. Summary and Overview

- We believe that we are successfully 'turning around' the process for these kinds of assessments by fully including the scientific community and the public in our efforts.
- Interacting with the public.
  - involving world-class scientists as principal authors.
  - held public meetings with industry, environmental groups, academia, and other government agencies.
- Recent scientific results continue to support the timeliness of the reassessment.
- Noncancer endpoints may be a more sensitive indicator of a response than cancer.
- Immunotoxicity and reproductive effects may be extremely sensitive responses.

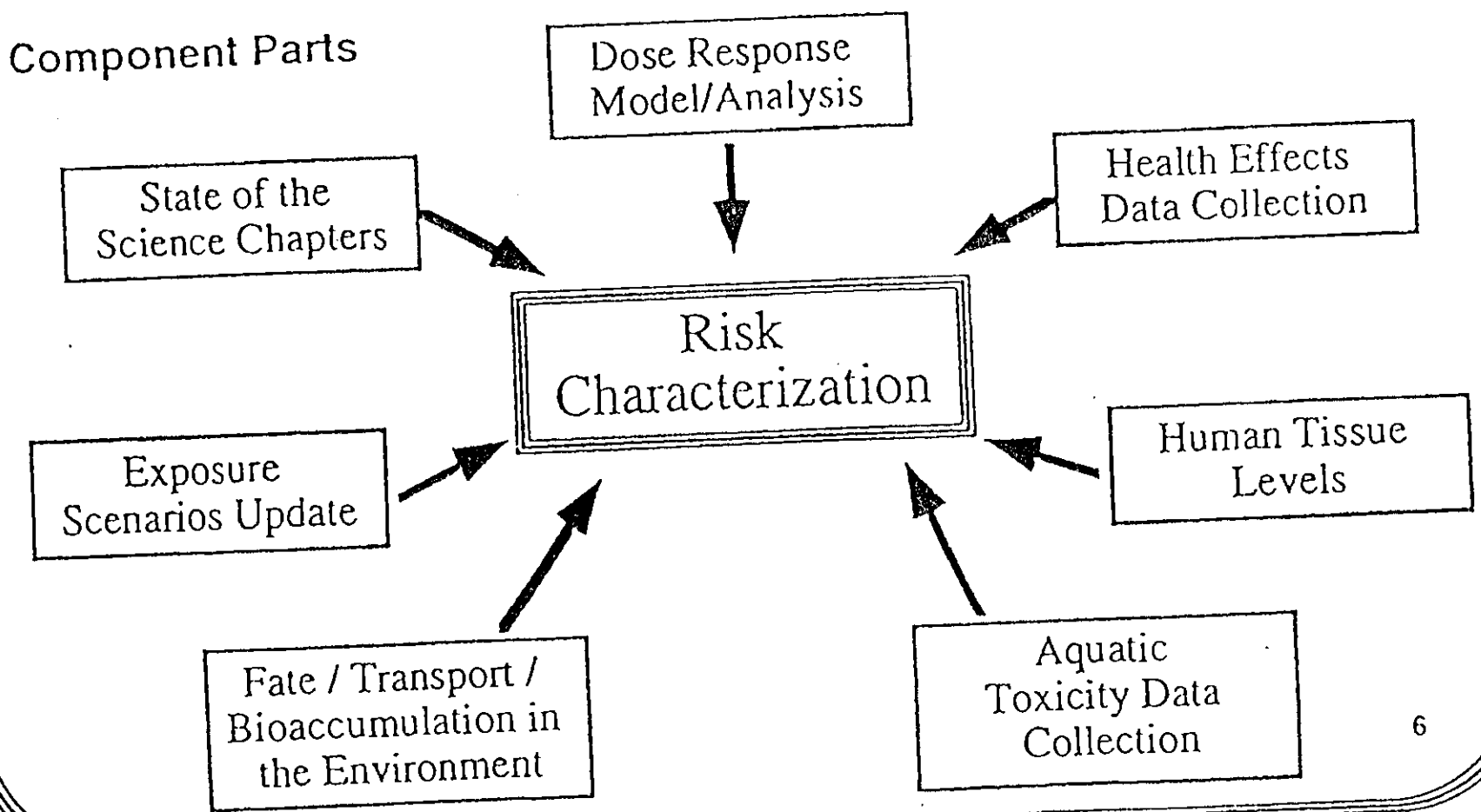
Summary and Overview....continued

- Dioxin-like PCBs are becoming of concern-we have developed an approach for dealing with them that we believe will satisfy the concerns of both environmental groups and industry.
- ORD scientists have reached the tentative conclusion that dioxin exposure may have been responsible for the decline of Lake Trout in Lake Ontario as a result of the reproductive toxicity of dioxin.

What Has Prompted This Reassessment?

Publication of Experimental Studies
and
Evolution in Scientific Thinking.

2. Where we are in the Dioxin Reassessment



The key changes from previous assessments of dioxin are:

- Direct involvement of the scientific community early in the process, and continuing efforts to reach scientific consensus about the risk characterization.
- A new dose-response model based on the mechanism of action.
- A better understanding of the mechanisms of action for toxic effects associated with these chemicals.
- Consideration of chemicals that exert toxic effects by the same mechanism as dioxin.

Revision to the Health Assessment Document: State-of-the-Science Chapters

- The external chapter authors are leading scientists in their fields.

- 7 Chapters: Toxicology, Reproductive/Developmental Effects, Carcinogenicity, Immunotoxic Effects, Pharmacokinetics, Epidemiology, Mechanism of Action.

- Most chapters have been completed in draft form, others will be completed within next few weeks.

- We anticipate meeting the schedule that we had presented to you previously.

Development of Dose/Response Model

- Basic Approaches:

  1. Evaluation of empirical data. (Top-down Approach)

  2. Theoretical considerations based on Mechanisms of Action.

  (Bottom-up Approach)

- Key Scientists who are developing the new model:

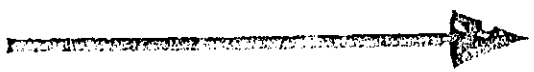
  * Dr. Michael Gallo and colleagues at the Robert Wood Johnson School of Medicine and Dentistry at Rutgers.

  * EPA biostatisticians and modelers.

  * Collaborators from NIEHS and other Federal Agencies, industrial, and academic sectors.

Dose/Response Relationships for Dioxin Effects

- Ligand Binding
  - Nuclear Occupancy
    - Enzyme Induction = Immunotoxicity
      - Reproductive Effects
        - Developmental Effects
          - Chloracne
            - Cancer



- Increasing Dose

Laboratory Support for the Dose / Response Assessment

- Conducted under direction of Dr. Linda Birnbaum, ORD Health Effects Research lab in collaboration with NIEHS, Texas A&M, UNC, and Duke.
- Comparison of the relative sensitivity of various dioxin responses with tissue burdens in rats and mice.
- Characterization of in vivo Toxic Equivalency Factors (TEFs) for co-planar PCBs
- Comparison of human liver levels of dioxin-like chemicals with induction of drug metabolizing enzymes.
- Analysis of dioxin-like compounds is a cooperative effort of ORD's Atmospheric Research and Exposure Assessment Lab in RTP, and OPP's Environmental Chemistry Lab at the Stennis Space Center, Bay St. Louis, MS.

Office of Research & Development

3-Phase Process for Review of the Chapters and Dose-Reponse Model

Phase 1: Completion of the state-of-the science chapters and the new dose-response model, and review of these products by peer review panel. April, 1992.

- *Objectives:*
  - To reach scientific consensus on information used and conclusions drawn in the chapters.
  - To reach scientific consensus on validity of model.
  - To reach scientific consensus on applicability of model.
  - Incorporate latest science, with a cut-off date of Dec. 31, 1991 for published information.
- *If no consensus is reached, decision must be made whether to proceed to risk characterization.*

Phase 2: Preparation of the risk characterization. May, 1995.

- *Objective:* Convene a group of scientists from outside EPA to discuss and formulate the critical points to be carried into the risk characterization. Our aim is to have the panel 'author' the risk characterization for us, to help us achieve consensus within the general scientific community.

- *Panel will develop risk characterization in 3 parts:*

  1. Characterize the risk (qualitatively and quantitatively) for 2,3,7,8-TCDD and related dioxins and furans,

  2. Characterize the risk qualitatively for co-planar PCBs, and determine if enough data exist to characterize the risk quantitatively,

  3. Combine the efforts in 1) and 2) to characterize the risks qualitatively and quantitatively, as appropriate.

Phase 3:

Review of the Risk Assessment by the SAB and the public.

- The risk characterization, the state-of-the science chapters, the chapter on the development of the model, and the exposure chapter will be brought to the SAB for review in the early Fall of 1992.

- Three components:

  SAB review and comment,
  Rewriting of reports as appropriate,
  Review of revised reports by SAB.

- Our aim is to complete this entire process by the Fall of 1993

3. ORD's Public Meeting on the Dioxin Reassessment

- In response to your request ORD held a public meeting November 15, 1991.
- Deputy Administrator Hank Habicht gave opening remarks, followed by introductory remarks by Erich Bretthauer.
- ORD officials formed a panel, and gave presentations explaining the key components of the process.
- 21 speakers representing industry groups, environmental groups, and academia signed-up to give oral presentations.
- About 250 people attended the one-day meeting.
- ORD received 30 written submissions from around the world, including new scientific information on human studies, mechanisms of action, and aquatic effects to be folded into the reassessment.

Other Public Events

- We have presented the science, and the scientific reassessment of dioxin at various scientific meetings including Dioxin '91, and the Toxicology Forum.
- We have met with API, NRDC, EDF, GE, and other interested parties to discuss our process and the status of the reassessment.
- We have met with CDC, NIOSH, NIEHS, Air Force to discuss future studies and the status of EPA's reassessent.
- We are planning additional public meetings and the publication of regular 'fact sheets' to continue our outreach efforts.
- The Department of Health and Human Services is planning to hold a 'consensus conference' on dioxin in the Fall. Originally scheduled for this spring, HHS has now decided to defer to EPA and wait for the current reassessment to be complete.

4. Recent Scientific Results and Conclusions.

- Dioxin does cause cancer in humans.
- Cancer may not be the most sensitive toxic response resulting from dioxin exposure. Immunotoxicity and reproductive effects appear to occur at body burdens that are approximately 100 times lower than those associated with cancer.
- Recent data indicate that there may not be a threshold for certain responses to dioxin. However, the implications for specific risk assessments, such as for cancer, are not yet clear.
- Recent evidence has strengthened the conclusion that the sensitivity of humans is similar to that of experimental animals (cancer, immunotoxicity, Ah receptor binding etc.).

New Science and Conclusions.....continued.

- Current exposure levels to dioxin and related compounds appear to place people at or near a body burden where sensitive responses may occur, especially for subpopulations at high-end of exposure, e.g., nursing infants, recreational and subsistence anglers.
- Continuing research into the risk from dioxin exposure should result in a continuing process of reassessment as new data become available and are incorporated into a new, more flexible, model.
- ORD scientists have reached the tentative conclusion that dioxin exposure may have been responsible for the decline of Lake Trout in Lake Ontario as a result of the reproductive toxicity of dioxin.

5. How Do We Deal With Other Dioxin-Like Chemicals, Including Certain PCBs?

- An issue for your attention concerns the inclusion in our reassessment of other chemicals, such as the co-planar PCBs, that may act by the same mechanism as dioxin.
- Many, if not all, scientists believe that all chemicals that act by the same mechanism as dioxin should be considered together.
- Some comments at our public meeting, particularly from industry, questioned whether or not the science had been sufficiently developed to permit inclusion of these chemicals in our assessment at this time.
- We plan to deal with this question explicitly, and separately, in our assessment, in order to resolve the questions to the extent that we can, as well as to prevent this controversy from "derailing" the major focus on dioxin.

6. Summary and Overview.

- We believe that we are successfully' turning around' the process for these kinds of assessments by fully including the scientific community and the public in our efforts.

Interacting with the public.

- involving world-class scientists as principal authors.

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Summary and Overview

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Appendix

State-of-the -Science Chapters...continued

5. DISPOSITION/PHARMACOKINETICS. Focus: Adsorption and bioavailabitiity after exposure; distribution in the body; metabolism and excretion; development of physlologlcally based pharmacokinetic model; pharmacokinetics in special populations.

Author: James Olson; Dept. Pharmacology and Therapeutics, SUNY, Buffalo, NY.

EPA Project Officer: Jerry Blancato, EMSL, Las Vegas, NV.

6. EPIDEMIOLOGY/HUMAN DATA. Focus: Recent studies evaluatlng carcinogenicity; literature review on non-cancer endpoints; human / anlmal comparisons.

Author: Charles Poole, Epidemiology Research Institute, Cambridge, MA.

EPA Project Officer: David Bayliss, Humar. Health Assessment Group.

7, MECHANISM (s) OF TOXIC ACTIONS. Focus: Receptor Interactions; transfer to the cell nucleus; DNA binding; impact on genetic activity.

Author: James Whitlock, Jr., Dept. of Pharmacology, Stanford Unlv. School of Med.

EPA Project Officer: William Farland, Director, Office of Health and Environmental Assessment.

Development of Dose/Response Model

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  1. Evaluation of empirical data. (Top-down Approach)
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- Key Scientists who are developing the new model:
  - *Dr. Michael Gallo and colleagues at the Robert Wood Johnson School of Medicine and Dentistry at Rutgers
  - *Dr. George Lucier and colleagues at NIEHS
  - *Dr. Mel Anderson at CIIT
  - *Dr. Ellen Silbergeld at University of Maryland
  - *EPA scientists