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BIOLOGICAL BASIS FOR RISK ASSESSMENT OF DIOXINS & RELATED COMPOUNDS

The Banbury Center, Cold Spring Harbor Laboratory, 21-24 October 1990

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October 19 1990

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HEALTH EFFECTS RESEARCH LABORATORY
RESEARCH TRIANGLE PARK
NORTH CAROLINA 27711

DATE: October 31, 1990

SUBJECT: Consensus at Banbury DIOXIN Conference

FROM: Linda S. Birnbaum, Ph.D., D.A.B.T.
Director, Environmental Toxicology Division, HERL, OHR (MD-68)

TO: Erich Bretthauer
Assistant Administrator, ORD (RD-672)

The Cold Spring Harbor Laboratory recently sponsored a Banbury Conference on "The Biological Basis for Risk Assessment of Dioxins and Related Compounds." The small workshop involved 38 participants from the United States, Canada, and Europe. Essentially all the "major actors" in the field of dioxin research, from analytical chemists, fate and transport researchers, exposure assessors, health scientists to risk assessors were present. Needless to say, the level of enthusiasm for the topic was high, as was the level of knowledge. Recent findings were presented and discussed in the light of their impact on our ability to intelligently assess risk.

Amazing as it might seem, consensus was reached on several major issues. The group seemed very comfortable with the conclusions that binding to the Ah (i.e., TCDD) receptor is necessary, but not sufficient, for all dioxin-induced effects. In fact, not only is ligand binding necessary but activation of the ligand/receptor complex and translocation into the nucleus is a prerequisite to any effects. Whether or not one wants to consider induction of cytochrome P450IA1 as a toxic response, it clearly IS an effect and appears to be the most sensitive response known. Therefore, at doses below where one can detect an induction of this enzyme, NO effects can occur. In other words, a "safe" dose can be equated with one at which no enzyme induction occurs.

The group also concurred that the tissue (at least liver) levels at which induction occurs is essentially the same in all species examined, i.e., within an order of magnitude. Based on these conclusions, "back of the envelope" calculations led to agreement that exposure to humans of 1-3 pg/kg/day would be essentially a NOEL. Coincidentally, this receptor-mediated mechanistic approach led to the same values as achieved using a standard safety factor/ADI approach.

Several other major issues were agreed upon. While species differences in TCDD sensitivity have often been stated as being a critical factor, this is really a misinterpretation of the weight of the data. While a given species may be an outlier for any given endpoint (lethality, chloracne, developmental toxicity, immunotoxicity, teratogenicity, death), no species is an outlier for all the responses. In fact, even for lethality where the species differences between the guinea pig and hamster is often referenced, all the other species examined have LD_{50} values clustered about 100 µg/kg.

...structural malformations, i.e., terata, will not be observed in human babies since the doses that would cause such abnormalities would also cause severe toxicity to the embryo/fetus and the mother. This is encouraging since deformed babies are one of the major concerns expressed by people (the other being cancer).

The remaining consensus is extremely important. Dioxin clearly has the potential to cause serious health effects. However, exposures, except in the few accidental poisoning episodes, have been low. As long as exposures do not increase, dioxin should not pose a health threat.

The major issue that did not receive adequate attention was that of TEFs. There is agreement that for compounds having the same mechanism of action, additivity is an appropriate approach to risk assessment. However, the determination of the appropriate TEF is still a subject for debate. There was some data presented that suggested that the TEFs based on acute exposures are not adequate for long-term scenarios. There was also much question about the use of TEFs for PCBs. I think that EPA is heading in the right direction by scheduling a RAF meeting in December to address this issue.

Please do not hesitate to contact me (FTS 629-2685) if I can provide additional information. I should point out that two other Agency scientists participated in this conference - Bill Farland of OHEA and Phil Cook of the Duluth laboratory.

cc: Dr. Larry Reiter
Dr. Ken Sexton
Dr. Bill Farland
Dr. Phil Cook

December 3, 1990

NAME
TITLE
OUTLET
ADDRESS

Dear NAME OF REPORTER:

From October 21 to 24, thirty-eight of the world's foremost experts on dioxin convened at the Banbury Center of Cold Spring Harbor Laboratory to examine the scientific data pertaining to dioxins. The goal of the scientists and policy-makers was to reach a consensus on how to assess human risk for dioxin exposure and to establish an acceptable daily human intake of dioxin.

The outcome of the consensus conference was a rejection of the linear model for human exposure to dioxin; this model is currently used in the United States. The experts agreed that a receptor-mediated model is more accurate. (A linear model assumes that any exposure constitutes a risk. The receptor-based model allows for the presence of a substance in the environment, with no risk experienced below a certain level of exposure.)

In light of the implications of the conference outcome for assessments of dioxin's risk and for regulatory decisions, each of the three scientific chairmen of the conference has prepared a press statement to provide you with information on the conference outcome. Proceedings of the conference will be published by Cold Spring Harbor Laboratory Press in Spring 1991.

The conference chairmen were Michael Gallo, PhD, professor and chief, Division of Toxicology, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School; Robert J. Scheuplein, PhD, director, Office of Toxicological Services, U.S. Food and Drug Administration; and Cornelius A. van der Heijden, PhD, director, Department of Toxicology, National Institute of Public Health, The Netherlands.

In addition to the three statements on the conference outcome, enclosed are a list of conference participants and a background document on dioxin. The background document has been prepared by conference participant George Carlo, PhD, JD, an epidemiologist at the State University of New York at Buffalo and chairman of the Health and Environmental Sciences Group, Washington, D.C.

Each of these four scientists is available to speak with you. I will call you shortly to see if I can provide assistance in this regard. Thank you.

Sincerely,

Nancy Mensch Turett
Senior Vice President

Statement on the outcome of The Banbury Conference "Biological Basis for Risk Assessment of Dioxins and Related Compounds"

From: Michael Gallo, PhD
Professor and Chief, Division of Toxicology
Environmental and Community Medicine
Robert Wood Johnson Medical School
Piscataway, NJ

Perhaps the most important outcome of this meeting is the fact that there was agreement that the model traditionally used to assess dioxin risk is no longer appropriate and that all toxic effects of dioxin appear to be receptor-mediated. In simple terms, this means that for dioxin to have an effect it must get to a specific site on the cell, bind to it, move into the cell nucleus, and bind to genetic material. Several thousand receptors must be occupied before any biological or toxic effect is seen.

With the receptor-mediated model, there is a dose level below which no biologically significant effects can occur. Thus, the receptor-mediated model differs greatly from the linearized multistage model (traditionally used to assess risk for dioxin and other chemicals), which implies that no level of dioxin is safe.

This conclusion -- that dioxin effects are receptor-mediated -- represents the evolution of expert thinking over the past twenty years, with continuous evaluation, re-evaluation and scrutiny of the data that have accumulated. Even a few years ago, there was good evidence that the linear model for risk assessment of dioxin was inappropriate, that the marked disparity between animal and human effects, and even among species, suggested a receptor-mediated mechanism. The conference also clarified the need for scientists to reach agreement on the proper risk model before they could appropriately assess whatever biological effects, if any, are posed by dioxin.

Now that consensus has been reached regarding the mechanism of dioxin's action, it will be possible to more specifically examine its action and more appropriately determine whether and how public policy should be affected.

Statement on the outcome of The Banbury Conference "Biological Basis for Risk Assessment of Dioxins and Related Compounds"

From: Robert J. Scheuplein, Ph.D.
Director
Office of Toxicological Sciences
Food and Drug Administration
Washington, D.C.

1990

The aim of this conference was to review the most recent biological data on dioxin and to discuss how this knowledge on the mechanism of dioxin toxicity can be incorporated into risk assessment -- particularly at low levels of exposure. The conference achieved consensus on several issues.

The group seemed comfortable with the conclusion that all the major toxic effects of dioxin; immunotoxicity, reproductive effects and cancer are mediated through the Ah receptor. The induction of the cytochrome p4501A1 enzyme system appears to be the most sensitive biological response of TCDD known. At doses below where this enzyme can produce effects, no effects can occur. Thus a "safe" dose for dioxin can in principle be established.

In reviewing the available epidemiologic data, including Viet Nam and Seveso, the conference participants agreed that, with the exception of chloracne, no human toxicity (including cancer and reproductive effects) can be reliably attributed to dioxin exposure from these known exposures.

Although there is no doubt that persistent dioxin exposure in the range of several nanograms per kilogram per day has the potential to cause serious health effects in animals, current human environmental levels are about a thousand times less -- a few picograms per kilogram per day. There was reasonable consensus that these low levels probably do not pose a health threat to humans.

There was some discussion concerning the appropriateness of the current regulatory levels established for dioxin. There was consensus that the receptor-based mechanisms be taken into account in risk assessment and there is a reasonable likelihood that when this is done that safe levels will be closer to the 1-10 picogram per kilogram range adopted by most European countries.

Statement on the outcome of The Banbury Conference "Biological Basis for Risk Assessment of Dioxins and Related Compounds"

From: Dr. C.A. van der Heijden
Director of Toxicology
National Institute of Public Health and
Environmental Hygiene
The Netherlands

The goal of this conference was to incorporate the most recent biological information pertaining to dioxins and related compounds in an effort to reach a consensus on how to assess risks associated with dioxin exposure, as well as to establish an acceptable daily intake of dioxin.

Participants agreed that all toxic effects observed in association with exposure to dioxin are receptor-mediated. Participants also agreed that the presence of detectable levels of a primary component of the drug metabolizing system in the liver, cytochrome P-450, is the first clear signal of dioxin toxicity and that there is no associated risk unless this enzyme can be detected.

The significance of this finding is that there is a dose level below which no biologically significant effects occur. This is in contrast to the linear models traditionally used, which theorize that even one molecule of dioxin can be sufficient to cause adverse health effects in humans. Conference participants agreed that the linear model should no longer be used to assess dioxin risk.

The outcome of this conference provides us with a much more precise way to assess any risks associated with dioxin and to begin to understand why data on human exposure to even large amounts of dioxin have consistently shown that little, if any, risk is posed, whereas, among some animals, dioxin continues to be shown as a potent carcinogen. Based on the receptor-mediated model and results from molecular biology research, there is, therefore, no evidence that levels of dioxin exposure below 1 pg/kg of body weight per day, as experienced by the general population, pose any risk.

Using the receptor-mediated model, a tolerable daily intake (TDI) of dioxin and related compounds would be between 1 pg/kg and 10 pg/kg body weight, when considering a no-effect level and safety factor of 100 (this is the approach most commonly used when determining acceptable levels of exposure. A safety factor of 10 could be employed if more specific physiological effects, such as those on liver enzymes, were known). Dealing with an estimated average exposure to dioxin and related compounds in industrialized countries of approximately 2 pg, one can conclude that current exposure is on the level of the suggested TDI (1pg/kg to 10pg/kg), so no risk for the population would be expected from background levels currently in the environment.

Malcolm Gladwell

The Wall Street Journal
Amal Naj - New York
Bruce Ingersoll - D.C.

Associated Press
Scott Sonner
Don Kendall - Ag. Dept

Time
Charles Alexander, Science Editor - N.Y.
Glen Garelik - D.C.

Newsweek
Mary Hager - D.C.
Sharn Begeley - N.Y.
Geoffrey Cowley - N.Y.

Environmental Reporter
Damon Chappie

Science
(Science writers do not have specific beats. The three below are the most likely to be interested in a story about toxic waste.)

Eliott Marshall
Leslie Roberts
David Hamilton

Scientific American
Jonathan Piel, editor

United Press International
George Lobsenz
Steve Gorman
Chuck Abbott - Ag. Dept.

Journals to Keep Informed

American Journal of Public Health
Alfred Yankauer, editor

New England Journal of Medicine
Dr. Arnold Relman, editor-in-chief

JAMA
Annette Flanagin