UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

April 26, 1985

OFFICE OF
THE ADMINISTRATOR

Honorable Lee M. Thomas
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Thomas:

On November 28-29, 1984, the Environmental Health Committee of EPA's Science Advisory Board reviewed a draft Health Assessment Document for Polychlorinated Dibenzo-p-dioxins, prepared by the Office of Health and Environmental Assessment (OHEA) in EPA's Office of Research and Development. The stated purpose of the draft document is to serve as a multimedia source to place adverse health responses in perspective and to provide a scientific basis for regulatory decisions by the Office of Air and Radiation.

The Committee recommends that the health assessment document primarily assess the effects of one isomer, 2,3,7,8-tetrachlorodibenzo-p--dioxin (TCDD). At present, only limited information exists on the health effects of other dioxins. For example, the draft document describes chronic bioassay information only for hexachlorodibenzo-p-dioxins besides TCDD. Moreover, questions have been raised about the bioassay of the hexachlorinated isomers for quality control reasons, and the document does not deal adequately with the uncertainty in the quantitative assessment of them. The Committee suggests that OHEA evaluate in a separate chapter the effects of those dibenzo-p-dioxin isomers for which sufficient data are available, relative to TCDD through multiple approaches, as outlined in the attached technical comments.

The Committee agrees with the conclusion in the document that, using the criteria of the International Agency for Research on Cancer (IARC), the animal evidence for carcinogenicity of TCDD is "sufficient." This information would place dioxins into either IARC category 2A or 2B. The draft document evaluates the weight of the evidence for carcinogenicity in humans as "limited." This information would place TCDD into IARC Group 2A. However, the Committee finds that the evidence for carcinogenicity of dioxins in humans is at best uncertain. Because the rationale to group tumors is not clear, we are unable to provide advice on the assignment of dioxins to category 2A or 2B. In addition, the evidence for fetotoxicity of TCDD has not been dealt with adequately in the document. Our other key findings and conclusions are summarized in the attached technical report.

OHEA has prepared multiple assessments of dioxins, not a single multimedia document. To avoid duplication and possible confusion, we suggest that OHEA prepare only one assessment document to serve the needs of all EPA programs unless it has a compelling reason to do otherwise.

With the revisions suggested here and in the technical comments, the document should be scientifically adequate for its stated purposes. We appreciate the opportunity to review the polychlorinated dibenzo-p--dioxins health assessment document and provide advice on this public health issue. We request a formal response to our advice.

Sincerely,

Richard A. Griesemer

Richard A. Griesemer, D.V.M., Ph.D.
Chair, Environmental Health Committee

Norton Nelson

Norton Nelson, Ph.D.
Chair, Executive Committee

cc: A. James Barnes (A-101)
Assistant Administrators

TECHNICAL REPORT OF THE ENVIRONMENTAL HEALTH COMMITTEE OF EPA's SCIENCE ADVISORY BOARD REGARDING A DRAFT HEALTH ASSESSMENT DOCUMENT FOR POLYCHLORINATED DIBENZO-p-DIOXINS

INTRODUCTION

On November 28-29, 1984, the Environmental Health Committee reviewed a draft Health Assessment Document for Polychlorinated Dibenzo-p-dioxins [EPA-600/8-84-014A; May 1984; External Review Draft]. The document was prepared by the Office of Health and Environmental Assessment (OHEA). The Committee's technical comments relating to chapters on different subjects are discussed below.

Overall, the draft document adequately interprets the scientific data base, and it is generally well organized. However, the Committee recommends that EPA not prepare multiple documents that evaluate the same substance without a compelling rationale. In the case of dioxins there are three extensive documents that essentially replicate each other. We suggest that OHEA consolidate these different versions into a single text. Specifically, we recommend that this document primarily assess the effects of one isomer, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The draft document describes chronic bioassay information only for hexachlorodibenzo-p-dioxins and TCDD. The bioassay of the hexachlorinated isomers is under review for quality control reasons, and the document does not deal adequately with uncertainty in the quantitative assessment of these isomers. The Committee suggests that OHEA evaluate in a separate chapter the potencies and effects of all dibenzo-p-dioxin isomers relative to TCDD through multiple approaches. Where sufficient data are available, the relative potency of each isomer can be described by reference to yield of TCDD by photochemical degradation, receptor binding affinity, short-term test results, structure-activity considerations (including degree of chlorination), and other bioassay information.

EXPOSURE

The document summarizes information on environmental levels in section 4.5. The Committee has been relying on the Office of Air Quality Planning and Standards (OAQPS) for information on exposure, usually in the form of a brief memo. OAQPS was unable to supply a memo for this document, and therefore the discussion of exposure was cursory. Strictly speaking, the draft document relates to the identification of hazard and evaluation of the dose-response relationship. The brief survey of exposure information in the document, however, was not sufficient to integrate with hazard information, neither was it possible to evaluate it with respect to the occurrence of health effects of dioxins in exposed human populations.

The draft document gives undue emphasis to the theory that dioxins are formed during combustion. Work by Czuczwa and Hites provides strong evidence against this theory.† The review of analytical chemistry needs to caution the reader regarding the reliability of the data. The bio-availability of dixons should be described. Although most of the toxicological data is available for 2,3,7,8-TCDD, exposure to this isomer is significantly less than for other isomers.

PHARMACOKINETICS

This chapter does not adequately review two competing hypotheses for the mechanism of dioxin action that are current within the scientific community. In particular, the document does not review the credibility of: (1) whether TCDD is biologically active without metabolic transformation (e.g. as a procarcinogen), or (2) whether TCDD activity is a consequence of production of a very potent metabolite.

GENERAL TOXICITY

The acute, subchronic and chronic toxicity sections are a scientifically defensible statement of the literature on dioxins, except in the area of neurotoxicity. OHEA may want to add separate sections on this subject and on "wasting syndrome." Overall, the summary does not adequately pull together the primary issues of the chapter, and the issue of where humans fit into the potency spectrum of species is not adequately addressed.

MUTAGENICITY

The evidence for mutagenic effects of dioxins is negative. This data has important implications for the quantitative estimate of carcinogenic risk, as described below.

TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

Fetotoxic effects of dioxins occur at doses similar to those at which carcinogenic effects occur. This information also may be of use in standard setting and deserves more emphasis in the document. As a general matter, the question of fetoxicity of TCDD has not been dealt with adequately.

CARCINOGENICITY

Do dioxins initiate, promote or both? The conceptual basis of OHEA's estimation porcedures are directed towards initiation. For dioxins, the known event is promotion, which is operationally defined by an increased incidence of liver tumors in laboratory animals pretreated with initiators.

† J.M. Czuczwa and R.A. Hites, "Environmental Fate of Combustion-Generated Polychlorinated Dioxins and Furans," Enviro. Sci. Tech. 18 (1984), 444-450.

Neither genetic nor DNA adduct evidence is available to support a mechanism of initiation through direct damage to the chromosome by TCDD. At some point the Agency will have to deal with this issue, even if it is only to explain the uncertainty in risk estimates.†

The evidence for carcinogenicity in laboratory animals is positive only in the sense of increasing background. The human data on tumors is questionable and, in particular, the Committee does not understand the rationale by which different kinds of human tumors have been aggregated. In addition, rodents respond to TCDD by increases in fibromas which do not increase in incidence among exposed humans. The document should point out this paradox.

The Agency's evaluation of the the effects of corn oil vehicle on bioassay results is simplistic and needs further emphasis.

QUANTITATIVE ESTIMATES OF RISK

OHEA should consider adding a quantitative estimate of fetotoxic potency. However, a linear dose-response model will not be plausible for fetotoxic effects. Late in embryogenesis many cells of a critical stage would have to be affected before a teratogenic effect in the fetus would occur. The Committee also has multiple concerns (as specified below) with the expression of the Agency's "plausible upper bound" estimate of carcinogenic potency for TCDD, as has been the case with health assessment documents for other substances. The Committee also concludes that:

° The definition of unit risk is not given correctly in the document because the values are incremental (not absolute) with respect to existing lifetime risk.

° The explanation of the plausible upper bound nature of the estimate is not consistent throughout the document. This concept needs careful expression in the Agency's documents since quantitative estimation remains a matter of some controversy and can be easily misunderstood. These comments and procedures can be more readily understood if the Agency's scientific review documents provide carefully written definitions and explanations of such terms.

° The justification of the linear dose-effect model for low dose extrapolation is not satisfactory (p. 11-102 to 11-104). Strictly speaking it should more carefully caveat the statement that the linear model has the "best scientific basis" among competing models for low-dose extrapolation of carcinogenic potency.

° The Agency's procedure to calculate risk estimates from animal data is to fit a nonlinear model (the multistage) and compute the largest linear term (in the sense of a 95% confidence limit) that is consistent with the data. This linear term will dominate in the calculation of the dose-effect relationship for low-dose extrapolation. The procedure is therefore appropriate for calculating a plausible upper bound estimate of effect that is linear in dose, but it is potentially misleading to describe the underlying model as linear.

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†I. Bernard Weinstein, "Dioxins as Carcinogenic Promoters," in William W. Lowrance, ed., Public Health Risks of the Dioxins, Rockefeller University, (1984), p. 155.

° The upper bound potency estimates based on animal data should be compared with upper confidence interval estimates of incidence from the available epidemiology data (both negative and positive) to see if there is consistency between estimates derived from the two data sources.

° An explanation of the tables should be provided for Appendix B. An additional appendix which gives an explanation of the International Agency for Research on Cancer (IARC) criteria, similar to the one for the cadmium assessment document, would be a useful reference.

° The Committee recommends that the text display the numerical formula both for the multistage model obtained with a maximum likelihood estimate and for the multistage model with the single hit expanded to give a plausible upper bound in a 95% confidence limit sense. At present, several tables give results from these models, and there is a general explanation on p. 11-104, but the actual formulas in use are not available for inspection.

° The document does not give lower-bound values comparable to the upperbound estimates. If the lower bound is zero, this should be stated.

° Since this is a source document, the reader will want to understand the uncertainty in the estimates. The Committee recommends that the Agency present maximum likelihood estimates in the discussion of the range of plausible estimates. The difference between the upper-bound and the maximum likelihood estimates should be clearly explained in the context of the multistage model and the assessment procedures used by EPA.

° The expression of uncertainty in the quantitative estimate for TCDD is an improvement over health assessment documents for other substances reviewed by the Committee. However, the treatment of the data for the hexachlorinated isomers could be improved. One option is to delete this estimate from the documents, since the bioassay evidence also is in question, due to quality control problems. Another option would be to provide many estimates, varying models and interpretation of pathology data, in the form of a sensitivity analysis.

° The time-to-tumor concept needs to be applied to the TCDD data base.

RANKING OF RELATIVE POTENCIES

The table of relative potencies and the accompanying histogram that illustrates the relative potencies of substances previously reviewed by the Carcinogen Assessment Group has been critized by the Committee in the review of health assessment documents for other substances. The Committee suggests that insertion of IARC categories for these substances into the Table will remedy some, but not all concerns with this data. The essence of the problem in comparing these potencies is the variable data on which the estimates are based, including the potential confusion between potency and severity, which is no different in principle than between potency and efficacy with pharmacological agents. Describing only potency overemphasizes the dose for a given incidence of an effect, without indicating the extent of evidence that the effect will occur. Columns could be added to the Table for other categories of biological information such as loss of life expectancy, malignancy, use of epidemiological or animal data. Instead of point estimates, ranges of potency also would prove informative.