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U.S. HOUSE OF REPRESENTATIVES

COMMITTEE ON SCIENCE

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July 10, 1996

Admiral E.R. Zumwalt, Jr.
USN (retired)
1000 Wilson Blvd.
Suite 3105
Arlington, VA 22209-3901

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Dear Admiral Zumwalt:

I would like to express my sincere appreciation for your testimony during the December 13, 1995 Energy and Environment Subcommittee hearing, "Scientific Integrity and Federal Policies and Mandates: Case Study III—EPA's Dioxin Reassessment".

Enclosed please find a copy of the complete hearing record from December 13, 1995. Thank you again for your valuable contribution to the hearing.

Cordially,

Dana Rohrabacher
Chairman
Subcommittee on
Energy and Environment

DR:jld

Enclosure

EPA

Testimony of
William H. Farland, Ph.D.
Director,
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
before the
Energy and Environment Subcommittee
of the
Committee on Science,
House of Representatives

December 13, 1995

Introduction

Scientists from the U.S. Environmental Protection Agency (USEPA), other Federal agencies and the general scientific community have been involved in a comprehensive scientific reassessment of dioxin and related compounds since 1991. External review drafts of the reassessment documents entitled "Estimating Exposure to Dioxin and Related Compounds" and "Health Assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds" were made available in September, 1994 by the Agency for public comment and review by the EPA's Science Advisory Board (SAB). This process has been a model for open, participatory environmental health assessment. Peer review has been an integral part of the entire reassessment process. Extensive comments have been received and will be the basis for revisions to the draft documents. These documents and subsequent comments highlight a number of issues which are of broad scientific interest. Answers to the questions posed on page 2 of the Hearing Charter are discussed in the text that follows. In brief, 1) the EPA believes that the risk characterization was consistent with the scientific findings contained in the earlier chapters; 2) contrary to the implication of the question, the risk characterization was informed by input from a panel of external reviewers of the draft chapters, drafted by Federal scientists and was peer reviewed. It, like the rest of the report, involved both EPA and non-EPA drafters and reviewers; 3) EPA's risk characterization does not rely solely on high levels of exposure to animals, but integrates animal data with limited human information. Animal data have been obtained at levels of exposure comparable to human exposures, and human information has been obtained on populations exposed at background levels and above; and 4) while regulatory impact assessments are carried out on every regulation that might be issued, no analysis of the potential economic impact on regulations that may be based on this reassessment will be conducted until the reassessment is complete and a comprehensive Agency-wide strategy has been developed.

Background

Dioxins are a group of chemical compounds inadvertently created through a number of activities including: combustion, certain types of chemical manufacture, chlorine bleaching of pulp and paper, and other industrial processes. Dioxin is produced in very small quantities compared to other pollutants (around 30 pounds TEQ[1] annually in the U.S.); however, because it is highly toxic, it has been treated as a significant environmental pollutant since the early 1970's. U.S. EPA first took action against dioxin as a contaminant of the herbicide 2,4,5-T in 1979. Since then, EPA has expanded its dioxin control efforts to each of its major programs.

In 1985 EPA published a scientific review of the health effects of 2,3,7,8-TCDD, the most toxic of the dioxin compounds. That assessment has served as the scientific basis for dioxin risk estimates for all U.S. EPA programs. In April 1991, EPA announced that it would conduct a comprehensive scientific reassessment of the health risks of exposure to the family of compounds generally known as dioxin (2,3,7,8-TCDD and other dioxin-like compounds, including certain dioxin-like polychlorinated biphenyls (PCBs)). EPA has undertaken this task in light of significant advances in our scientific understanding of mechanisms of dioxin toxicity, significant new studies of dioxin's carcinogenic potential in humans, and increased evidence of other adverse health effects. The reassessment is part of the Agency's goal to improve its research and science base and to incorporate this knowledge into EPA decisions. In September, 1994, EPA released a "public review draft" of its dioxin reassessment. This release marked a mid-point in EPA's effort to reevaluate the scientific understanding of dioxin. While the reassessment has been underway, EPA has continued to move forward in implementing its dioxin control programs, based on the 1985 assessment and, in most cases, applying technology-based rather than risk-based solutions. In the past fifteen years, EPA has taken action under every one of its major statutes to control the risks of dioxin. No regulatory action has been undertaken by the Agency based on the results of this draft reassessment. Throughout the reassessment process the Agency has repeatedly stated that existing EPA efforts and programs will not be changed on the basis of this draft reassessment, but they may change significantly after the completion of the report.

1TEQ = Toxic Equivalents. TEQ is an internationally recognized convention for expressing the toxicity of a complex mixture of multiple dioxin-like compounds, varying in their toxicity, as an equivalent amount of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the reference compound for this class.

Science Reassessment

In September 1994, the EPA released the public review draft of the full reassessment. The reassessment consists of two documents, each about a thousand pages long, and each published in several volumes. One of these documents addresses the human health effects of dioxin; the second focuses on sources and levels of exposure. The reassessment is a scientific document and does not address regulatory policy or issues. An effort to address regulatory policy issues raised by the reassessment will be carried out in separate, public discussions in the winter and spring of 1996. Volume three of the health effects document is the Risk Characterization chapter . This chapter integrates the findings of both the effects and exposure documents, outlines important inferences and science policy assumptions made in the absence of complete information, and describes the potential hazards and risks posed by dioxin.

The draft study not only updates the 1985 document, but also represents an ongoing process to build a broad scientific consensus regarding the question of dioxin's potential to produce toxic effects . To help foster this consensus, EPA has worked to make each phase of the dioxin reassessment an open and participatory process. These efforts have included the involvement of outside scientists as principal authors of several chapters, numerous public meetings to take comment on our plans and progress, and publication of earlier drafts of our work for public comment and review. The current "external review" draft has been made available for public comment and full scientific review. Results of this review, which took place from September, 1994 to October, 1995, will be used to revise and update the drafts over the next year. When this process is completed, we anticipate having an up-to-date and thorough scientific evaluation of dioxin that is at the cutting edge of environmental toxicology and exposure assessment.

Regarding health risks, the draft study reaffirms the association of dioxin and cancer. In its 1985 assessment, EPA concluded that dioxin is a proven animal carcinogen and a probable human carcinogen. The current draft report reaches the same conclusion, but with greater confidence because of additional published human data and enhanced understanding of dioxin's mode of action. Based upon both animal and human evidence, EPA's estimate of dioxin's cancer potency is essentially unchanged from that of 1985.

The draft reassessment differs significantly from the 1985 document in its evaluation of dioxin's non-cancer effects. Today we have a stronger body of evidence to suggest that at some dose, dioxin exposure can result in a number of non-cancer effects in humans, and that some of these effects may have an adverse impact on health. These effects may include developmental and reproductive effects, immune suppression, and disruption of regulatory hormones. We currently have very limited

direct evidence to show that any of these non-cancer effects occur in humans at everyday levels of exposure. However, we can infer from the information on levels of dioxin and related compounds in the environment, in food, and in people that average everyday exposures are close to exposures that are known to cause such effects in laboratory animals. Humans exposed to dioxins at several times average background levels in the general population have also shown indications of subtle effects which may or may not represent an adverse impact on their health.

U.S. Exposure Survey

The Exposure Document provides the first comprehensive survey of U.S. sources of dioxin and related compounds. A large variety of sources of dioxin have been identified and others may exist. The available information suggests that the presence of dioxin-like compounds in the environment has occurred primarily as a result of industrial practices and is likely to reflect changes in release over time. The principal identified sources of environmental release may be grouped into four major types: combustion and incineration sources; chemical manufacturing/processing sources; industrial/municipal processes; and reservoir sources. Although the current draft suggests that municipal and hospital waste incineration may account for the majority of known releases, comments suggest the need to reduce these estimates based on changes in numbers of active facilities and technologies applied to incineration in the past few years. Also, additional sources have been identified and will be further addressed in future versions of the document.

Because dioxin-like chemicals are persistent and accumulate in biological tissues, particularly in animals, the scientific community has hypothesized since the late 1980's that the major route of human exposure is through ingestion of foods containing minute quantities of dioxin-like compounds. The EPA reassessment document adopts this hypothesis. This pathway results in wide-spread, low-level exposure of the general population to dioxin-like compounds. Certain segments of the population may be exposed to additional increments of exposure by being in proximity to point sources or because of dietary practices. The actual levels of dioxin and related compounds in the environment and in food in the U.S. are based on relatively few samples and must be considered quite uncertain. However, they seem consistent with levels measured in a number of studies in Western Europe and Canada. The consistency of these levels across industrialized countries provides reassurance that the U.S. estimates are reasonable. Collection of additional data to reduce uncertainty in U.S. estimates of dioxin-like compounds in the environment and in food represents an important data need. Data collection is currently underway in a series of studies being carried out by EPA and U.S.Department of Agriculture (USDA) scientists. Recent data on levels of dioxin-like compounds in the fat of beef suggests similar, if not slightly lower, levels compared to previous information. Additional food products are being collected and dioxin levels are being analyzed.

Air to Food Hypothesis

This assessment adopts the hypothesis that the primary mechanism by which dioxin-like compounds enter the terrestrial food chain is via atmospheric deposition. Dioxin and related compounds enter the atmosphere directly through air emissions or indirectly, for example, through volatilization from land or water or from re-suspension of particles. Deposition can occur directly onto soil or onto plant surfaces. At present, it is unclear whether atmospheric deposition represents primarily current contributions of dioxin and related compounds from all media reaching the atmosphere, or whether it is past emissions of dioxin and related compounds which persist and recycle in the environment. Understanding the relationship between these two scenarios will be particularly important in understanding the relative contributions of individual point sources of these compounds to the food chain and assessing the effectiveness of control strategies focussed on either current or past emissions of dioxins in attempting to reduce the levels in food. Commentors have also highlighted the importance of better understanding atmospheric transformation processes in order to adequately model fate and transport of these compounds from source to receptor (human or ecological).

Toxicity Equivalents

Because the assessment of dioxin and related compounds involves the evaluation of approximately eighteen major persistent chemicals and hundreds of others, often occurring as complex environmental mixtures, an approach has been developed to overcome the lack of information on individual members of this class. Throughout the reassessment, concentrations of dioxin and related compounds have been presented as TCDD equivalents (TEQs). TCDD is the best studied of this class of compounds and is the reference compound with regard to determination of toxicity equivalence factors (TEFs). Other dioxin-like compounds are assigned TEFs based on inspection of available physical, chemical and toxicologic information. Other approaches to evaluating the toxicity of dioxin-like compounds such as assuming that all are as toxic as 2,3,7,8-TCDD, or assuming that they do not contribute significantly to the toxicity of this family of compounds given 2,3,7,8-TCDD's potency are generally considered to be unacceptable. Therefore, the international scientific community, as represented by World Health Organization (WHO) and NATO scientific committees, the EPA and several states have adopted the TEF approach as a useful, albeit uncertain, procedure in the face of incomplete data on this family of compounds, and with the prospects of ever filling all of the data gaps improbable.

The strengths and weaknesses as well as the uncertainties associated with the TEF/TEQ approach have been discussed in detail in the documents but further attention will be needed to provide appropriate perspective on their use. In particular,

additional care will be given to delineating the contribution of TCDD, the best studied of these compounds, to estimated TEQ. The assessment of toxicity of dioxin and related compounds presents a difficult "complex mixture" problem. Use of the TEFs for dioxin-like PCBs in estimating total TEQ has received extensive comment. As noted, the use of the TEQ approach is fundamental to the evaluation of this group of compounds and as such represents a key assumption upon which many of the conclusions in this reassessment hinge. Additional data are being collected to evaluate this issue both in terms of the assignment of appropriate TEFs and in addressing issues such as additivity of the TEFs in environmental samples and food or in human blood, tissue, or mother's milk.

"Background" Exposure

The term "background" exposure has been used throughout this reassessment to describe exposure of the general population, who are not exposed to readily identifiable point sources of dioxin-like compounds. Data on human tissue levels suggest that body burden levels among industrialized nations are reasonably similar. Average background exposure leads to body burdens in the human population which average 40-60 pg TEQ/g lipid (40-60 ppt) when all dioxin-like dioxins, furans and PCBs are included. High-end estimates of body burden of individuals in the general population (approximately the top 10% of the general population) without additional identifiable exposures may be approximately 2 times higher based on available data. While there are some recent data to suggest that both environmental and human body burdens are on a downward trend, additional information will be needed to establish a baseline upon which to evaluate future measurements.

In addition to general population "background" exposure, some individuals or groups of individuals may also be exposed to dioxin-like compounds from discrete sources or pathways locally within their environment. Examples of these "special" exposures include: occupational exposures, direct or indirect exposure to local populations from discrete sources, exposure to nursing infants from mother's milk, or exposures to subsistence or recreational fishers. Although daily exposures to these populations may be significantly higher than daily exposures to the general population, simply evaluating these exposures by averaging higher daily intakes pro-rated over a lifetime might obscure the potential significance of elevated exposures for these sub-populations, particularly if exposures occur for a short period of time during critical times during development and/or growth. This has raised the issue as to the most appropriate "dose metric" to use for dioxin exposure. Exposure levels, intake values, and body burdens have all been used in the past for this purpose. While the current document focusses on body burden, it recognizes that other metrics of exposure may be more appropriate for assessing certain biological responses. In response to a number of comments on this issue, future versions of the report will address this issue more fully.

Mode of Action

This reassessment concludes that the scientific community has identified and described a series of events attributable to exposure to dioxin-like compounds including biochemical, cellular and tissue-level changes in normal biological processes. Binding of dioxin-like compounds to a cellular protein called the "Ah receptor" represents the first step in a series of common biological steps and may be necessary for most if not all of the observed effects of dioxin and related compounds in vertebrates including humans. While binding to the Ah receptor appears to be necessary for all well-studied effects of dioxin, it is not sufficient, in and of itself, to elicit these responses. Many effects elicited by exposure to 2,3,7,8-TCDD are shared by other chemicals which have a similar structure and Ah receptor binding characteristics. This is the main basis for the assumed validity of the TEF approach. Consequently, the biological system appears to respond to the cumulative exposure of Ah receptor-mediated chemicals rather than to the exposure to any single dioxin-like compound. Based on our understanding of dioxin mechanism(s) to date, it is accurate to say that interaction with the Ah receptor is necessary, that the Ah receptor in humans is similar in structure and binding characteristics to those found in dioxin responsive animals, and that there is likely to be a variation between and within species and between tissues in individual species based on differential responses "down stream" from receptor binding. The potency and fundamental level at which these compounds act on biological systems is analogous to several well studied hormones. Dioxin and related compounds have the ability to alter the pattern of growth and differentiation of a number of cellular targets by initiating a series of biochemical and biological events resulting in the potential for a spectrum of responses in animals and humans. Initial simplistic attempts to describe dioxin's mode of action as a transcriptional regulator of gene activity fail to account for recent data that suggests that receptor binding may also alter levels of cellular phosphorylation and hormone and growth factor receptor function without impacting transcription. Further work will be needed to understand this complex of inter-related activities. Additional data available to address these issues will be discussed in revisions to the reassessment document.

The reassessment also finds that there is adequate evidence based on all available information, including studies in human populations as well as in laboratory animals and from ancillary experimental data, to support the inference that humans may have the potential to respond with a broad spectrum of effects from exposure to dioxin and related compounds, if exposures are high enough. These effects will likely range from adaptive changes at or near background levels of exposure to adverse effects with increasing severity as exposure increases significantly above background levels. Enzyme induction, changes in hormone levels and indicators of altered cellular function represent examples of effects of unknown clinical significance and which may or may not be early indicators of toxic response. Induction of activating/metabolizing enzymes at or near background levels, for instance, may be adaptive or may be considered

adverse since induction may lead to more rapid metabolism and elimination of potentially toxic compounds, or may lead to increases in reactive intermediates and may potentiate toxic effects. Demonstration of examples of both of these situations for dioxins and for other families of compounds is available in the published toxicologic literature. Clearly adverse effects including, perhaps, cancer may not be detectable until exposures exceed background by one or two orders of magnitude (10 or 100 times) or more. The mechanistic relationships of biochemical and cellular changes seen at very low levels of exposure to production of adverse effects detectable at higher levels remains uncertain and controversial. It is this relationship in conjunction with an understanding of "background" exposures to dioxin-like compounds that is at the heart of this assessment.

Species Sensitivity

It is well known that individual species vary in their sensitivity to any particular dioxin effect. Human data provide direct or indirect support for evaluation of likely effect levels for several of the endpoints based primarily on animal information although the influence of variability among humans remains difficult to assess. Biochemical, cellular, and organ-level endpoints have been shown to be affected by TCDD, but specific data on these endpoints do not generally exist for other members of this chemical family. Despite this lack of specific data, there is reason to infer that these effects may occur for all dioxin-like compounds, based on the concept of toxicity equivalence.

Some of the effects of dioxin and related compounds such as enzyme induction, changes in hormone levels and indicators of altered cellular function have been observed in laboratory animals and humans at or near body burden levels of people in the general population. Other effects are detectable only in highly exposed populations, and there may or may not be a likelihood of response in individuals experiencing lower levels of exposure. Adverse effects associated with temporary increases in dioxin blood levels based on short term high level exposures, such as those that might occur in animal experiments, an industrial accident or in infrequent contact with highly contaminated environmental media, may be dependent on exposure coinciding with a window of sensitivity of biological processes.

Non-Cancer Health Effects

In TCDD-exposed men, subtle changes in biochemistry and physiology such as enzyme induction, altered levels of circulating reproductive hormones, or reduced glucose tolerance, have been detected in a limited number of the few available studies. These findings, coupled with knowledge derived from animal experiments, suggest the potential for adverse impacts on human metabolism, and developmental and/or reproductive biology, and, perhaps, other effects in the range of current human exposures. Given the assumption that TEQ intake values represent a valid comparison

with TCDD exposure, some of these adverse impacts may be occurring at or within one order of magnitude of average background TEQ intake or body burden levels. It seems reasonable to infer that, as body burdens increase within and above this range, the probability and severity as well as the spectrum of human non-cancer effects most likely increases. It is not currently possible to state exactly how or at what levels humans in the population will respond, but the margin-of-exposure (MOE) between background levels and levels where effects are detectable in humans in terms of TEQs is considerably smaller than previously estimated. These facts and assumptions lead to the inference that some more highly exposed members of the general population or more highly exposed, special populations may be at risk for a number of adverse effects including developmental toxicity based on the inherent sensitivity of the developing organism to changes in cellular biochemistry and/or physiology, reduced reproductive capacity in males based on change in hormone levels and, perhaps, decreased sperm counts, higher probability of experiencing endometriosis in women, reduced ability to withstand an immunological challenge and others. This inference that more highly exposed members of the population may be at risk for various non-cancer effects is supported by observations in animals, by scientific inference, and by some human information from highly exposed cohorts.

The deduction that humans are likely to respond with non-cancer effects from exposure to dioxin-like compounds is based on the fundamental level at which these compounds impact cellular regulation and the broad range of species which have proven to respond with adverse effects. Since, for example, developmental toxicity following exposure to TCDD-like congeners occurs in fish, birds, and mammals, it is likely to occur at some level in humans. It is not currently possible to state exactly how or at what levels people will respond with adverse impacts on development or reproductive function. Fortunately, there have been few human cohorts identified with TCDD exposures in the high end of the exposure range, and when these cohorts have been examined, few clinically significant effects were detected. The lack of adequate human information and the focus of most currently available epidemiologic studies on occupationally, TCDD-exposed adult males makes evaluation of the inference, that non-cancer effects associated with exposure to dioxin-like compounds may be occurring, difficult. It is important to note, however, that when exposures to very high levels of dioxin-like compounds have been studied, such as in the Yusho and Yu-Cheng cohorts, a spectrum of adverse effects have been detected in men, women and children. Some have argued that to deduce that a spectrum of non-cancer effects will occur in humans in the absence of better human data overstates the science; most scientists involved in the reassessment as authors and reviewers have indicated that such inference is reasonable given the weight-of-the-evidence from available data. As presented, this logical conclusion represents a testable hypothesis which may be evaluated by further data collection.

Development of Margins-of-Exposure (MOE)

The likelihood that non-cancer effects may be occurring in the human population at environmental exposure levels is often evaluated using a "margin-of-exposure" (MOE) approach. A MOE is calculated by dividing the human-equivalent animal LOAEL or no observed adverse effect level (NOAEL) with the human exposure level. MOEs in the range of 100 -1000 are generally considered adequate to rule out the likelihood of significant non-cancer effects occurring in humans based on sensitive animal responses. The average levels of intake of dioxin-like compounds in terms of TEQs in humans described above would result in body burdens well within a factor of 100 of levels representing lowest observed adverse effect levels (LOAELs) in laboratory animals exposed to TCDD or TCDD equivalents. Our analysis of body burdens in animals and humans relative to effect levels for a number of biochemical, cellular and clearly adverse endpoints has recently been published (DeVito, et al.,1995, Environmental Health Perspectives, Volume 103, Number 9) For several of the effects noted in animals, a MOE of less than a factor of ten, based on intake levels or body burdens, is likely to exist. Based on these data alone, traditional toxicologic approaches for deriving likely NOAELs for humans and translating them into "safe" or "tolerable" levels for regulatory purposes will need to be reconsidered. While it is unlikely that any large segment of the human population is incurring an adverse impact from current body burdens, MOEs are less than we once believed. This issue has been recognized by the WHO and an expert panel has recently (November, 1995) been convened to consider the need to re-evaluate the WHO statement regarding a "tolerable daily intake" or TDI for dioxin and related compounds. A report of this meeting will be available in the very near future.

Carcinogenicity of Dioxin-Like Compounds

With regard to carcinogenicity, EPA's weight-of-the-evidence evaluation suggests that dioxin and related compounds (CDDs, CDFs, and dioxin-like PCBs) are likely to present a cancer hazard to humans. Extension of this statement of hazard to this broad range of compounds based on TEFs and in the face of limited data to assess cancer hazard of the individual congeners is a critical issue. The epidemiological data alone are not yet deemed sufficient to characterize the cancer hazard of this class of compounds as being "known." However, combining suggestive evidence of recent epidemiology studies with the unequivocal evidence in animal studies and inferences drawn from mechanistic data supports the characterization of dioxin and related compounds as likely cancer hazards, that is, likely to produce cancer in some humans under some conditions. It is important to distinguish this statement of cancer hazard from the evaluation of cancer risk. The extent of cancer risk will depend on such parameters as route and level of exposure, overall body burden, dose to target tissues, individual sensitivity, and hormonal status.

While major uncertainties remain, efforts of this reassessment to bring more data into the evaluation of cancer potency have resulted in an upper bound, risk specific dose estimate (1 X 10^{-6} risk or one additional cancer in one million exposed) of approximately 0.01 pg TEQ/ kg body weight/ day. Estimates of exposure associated with other specific risk values (10^{-5}, 10^{-4},etc.) can be derived by using a low dose linear model. These risk specific dose estimates represent plausible upper bounds on risk based on the evaluation of animal and human data. These values are similar to previous estimates published by EPA in 1985 but which were based on less data. "True" risks are not likely to exceed these values, may be less, and may even be zero for some members of the population. It is currently not possible to estimate more precisely the risk to exposed individuals. The use of a linear model to provide probabilistic risk estimates remains controversial. Alternative approaches will need to be addressed in future versions of the reassessment. The SAB specifically suggested that the dose-response discussion in Chapter 8 should reflect consideration of alternative models, including those inferring a threshold for response, and their implications on estimates of cancer risk.

The current evidence suggests that both receptor binding and some early biochemical events such as enzyme induction are likely to demonstrate low-dose linearity. The mechanistic relationship of these early events to the complex process of carcinogenesis remains to be established. If these findings imply low-dose linearity in biologically-based cancer models under development, then the probability of cancer risk will be linearly related to exposure to TCDD at low doses, and the slope of the response curve in the low dose region will be a critical issue for predicting risk. If they do not, non-linear relationships may exist between exposures and cancer risk. Until the mechanistic relationship between early cellular responses and the parameters in biologically based cancer models is better understood, the shape of the dose-response curve for cancer in the low-dose region can only be inferred with uncertainty.

Associations between human exposure to dioxin and certain types of cancer have been noted in occupational cohorts with average body burdens of TCDD approximately 2 orders of magnitude (100 times) higher than average TCDD body burdens in the general population. The average body burden in these occupational cohorts level is within 1-2 orders of magnitude (10-100 times) of average background body burdens in the general population in terms of TEQ. Thus, there is no need for large scale low dose extrapolations since these body burdens are the result of occupational exposures added to "background" exposures experienced by the general population. Nonetheless, the relationship of apparent increases in cancer mortality in these populations to calculations of general population risk remains uncertain due to uncertainty in the dose-response relationship within these two orders of magnitude.

TCDD has been clearly shown to increase malignant tumor incidence in laboratory animals (e.g. liver, lung, thyroid, hard palate). It also appears to decrease

the incidence of some hormone-sensitive cancers (uterine, mammary) in laboratory rodents. The reason for this decrease is unknown although some have speculated that it is due to dioxin's anti-estrogenic activity, while others have suggested that it is an indirect consequence of change in animal body weights. In addition, a number of studies analyzed in this reassessment demonstrate other biological effects of dioxin related to the process of carcinogenesis. A number of reviewers including some scientists on the SAB suggest that the complex impacts of dioxin on the carcinogenic process, causing the potential for both increases and decreases in cancer risk in exposed humans, need to be addressed if we are to truly appreciate the impact of dioxin exposures. Initial attempts to construct a biologically-based model for certain dioxin effects as a part of this reassessment will need to be continued and expanded to accommodate more of the available biology relating to potential cancer risk. In addition, biologically-based models to apply to a broader range of potential health effects associated with exposure to dioxin-like compounds will be needed in the future.

Risk Characterization

According to the National Research Council, who articulated the widely used risk assessment paradigm in their seminal, 1983 treatise on risk assessment in the Federal Government, risk characterization is the final step in the risk assessment process in which the first three steps (hazard identification, dose-response assessment and exposure assessment) are summarized and the information integrated to develop a qualitative or quantitative estimate of the likelihood that any of the hazards associated with the agent of concern will be realized in exposed people. In this step, strengths and weaknesses of the available data are discussed, and assumptions and uncertainties which are embodied in the risk assessment are articulated. This guidance has been re-iterated by the EPA in its own risk characterization policy on a number of occasions.

The risk characterization (Chapter 9) for dioxin and related compounds was developed as an integrated analysis of information from the exposure document and from the eight health effects chapters. Key assumptions were identified and discussed. Uncertainties attendant to the findings of the report were highlighted in the integrated analysis and in the risk characterization summary. Issues to be discussed in the risk characterization chapter emerged directly from the previous assessment work carried out by external authors as well as EPA scientists, were articulated by commentors on the process of reassessment in numerous public meetings, and specifically came from recommendations made by peer reviewers of the earlier versions of the reassessment chapters in 1992. This process led to the development of a draft risk characterization, primarily by EPA authors but with the assistance of some outside scientists. This early draft was reviewed extensively within the EPA and by numerous Federal agencies. The inter-agency review resulted in the formation of a drafting team from EPA, HHS, and USDA to address the comments of the reviewers. An unauthorized and unintended release of the inter-agency review draft also produced a round of

unsolicited external comments in June and July, 1994. All of this input formed the basis for the external review draft of the risk characterization which was released in September, 1994 for broad public comment and peer review by the Agency's SAB. Despite the question raised in the charter for this hearing, the risk characterization is consistent with the findings contained in the earlier chapters. Any minor inconsistencies identified by peer review will be rectified in the revised version of the document.

In its October, 1995 report to the Administrator, the SAB noted a number of strengths in the risk characterization. First, "by focusing serious attention on various non-cancer effects, the Agency has dispelled any mis-impression that EPA's risk assessment process is overly preoccupied with carcinogenic effects". Second, "by evaluating an entire group of compound classes (with a common attribute), rather than a single compound, the Agency responds to the generally mistaken criticism that its risk assessment process can only address issues on a chemical-by-chemical basis." Third, "in the opinion of most Committee Members, a useful comparative perspective is provided in the draft conclusions where the Agency highlights the margin of safety (between background exposures and levels of exposure where effects have been seen in test animals) for dioxin-like compounds is smaller than EPA usually sees for many other compounds."

On the other hand, the SAB noted three "major weaknesses." First, "the presentation portrayed in the draft conclusions is not balanced." This statement was footnoted with the following: "Several members of the Committee do not agree with this statement and regard the EPA presentation and the inferences drawn as appropriately conservative within the context of public health protection." Second, "important uncertainties associated with the Agency's conclusions are not fully recognized and subjected to feasible analyses." Third, "the characterization of non-cancer effects is not performed in a manner that allows meaningful analysis of the incremental benefits of risk management alternatives." This statement was footnoted with the following statement: "A minority within the Committee finds the non-cancer risk characterization to be appropriate for use within a public health perspective. However, they agree that the reassessment document's characterization is not performed in a manner which will be very useful in the analysis of the incremental benefits of risk management alternatives by those who will also be concerned with the micro-level incremental costs." These comments with their specified examples as well as more specific comments on the other chapters will be dealt with in the revision process.

Next Steps

The EPA is now in the process of addressing comments on the external review draft of the dioxin reassessment. Comments from the SAB will be considered along with those from the broader scientific community and the public who reviewed the report during the public comment period which extended from September, 1994 to January,

1995. The exposure documents and the first seven chapters of the health assessment document will be revised an updated by EPA Chapter Managers. As suggested by the SAB, summaries are being prepared for each of the health assessment chapters and the contribution of 2,3,7,8-TCDD or other dioxin-like compounds are being delineated so that a greater appreciation of the uncertainty in applying TEQ to complex mixtures can be gained. These revised portions of the document will be subjected to additional internal and limited external peer review prior to being finalized. A disposition of comments will be prepared as the documents are completed. Chapter 8 (Dose-Response Chapter) is being subjected to a major re-write as suggested by the SAB. This re-write will be drafted by an expanded dose-response modeling team, which will include additional statistical expertise and the assistance of a pharmacologist familiar with modeling receptor-mediated responses. The revised Chapter 8 will be subjected to a public peer panel review, containing 8-10 external scientific experts, prior to being finalized, and will be referred back to the SAB for review as suggested. The Risk Characterization will also be extensively revised to address public and SAB comments. As suggested by the SAB, public input on the revision process has been sought, additional experts from outside the Federal government will be enlisted to contribute to the revision, and a public peer review of the revised risk characterization by approximately 10 external scientific experts will be conducted prior to its finalization. The risk characterization will also be referred back to the SAB as suggested. The SAB can then evaluate response to their suggestions and the adequacy of the additional peer review conducted on the draft report.

With regard to the timing of these events, the revision process has already begun. Drafting of chapter summaries and the revised dose response chapter and the risk characterization are anticipated to be complete by March, 1996. Peer panel meetings are expected to be held in early May. Documents will be referred to the SAB in June with a review meeting to be held as soon as possible thereafter. Final documents are targeted for printing in August with release occurring in September, 1996. Obviously, this assumes that no major new issues arise during the revision process that would require extensive additional analysis or obviate the current approach to assessing dioxin risk.

Summary

Based on all of the data reviewed in this reassessment and scientific inference, a picture emerges of TCDD and related compounds as potent toxicants in animals with the potential to produce a spectrum of effects in animals and, perhaps, in humans. Some of these effects may be occurring in humans at very low levels, and some may be resulting in adverse impacts on human health. The potency and fundamental level at which these compounds act on biological systems is analogous to several well-studied hormones. Dioxin and related compounds have the ability to alter the pattern of growth and differentiation of a number of cellular targets by initiating a series of

biochemical and biological events resulting in the potential for a spectrum of responses in animals and humans. Despite this potential, there is currently no clear indication of increased disease in the general population attributable to dioxin-like compounds. The lack of a clear indication of disease in the general population should not be considered strong evidence for no effect of exposure to dioxin-like compounds. Rather, lack of a clear indication of disease may be a result of the inability of our current data and scientific tools to directly detect effects at these levels of human exposure. Several factors suggest a need to further evaluate the impact of these chemicals on humans at or near current background levels. These are: the weight of the evidence on exposure and effects; an apparently low margin-of-exposure for non-cancer effects; and potential for additivity to background processes related to carcinogenicity. Critical issues relating to dioxin exposure and toxicity, and requiring additional attention in the reassessment include: sparse data to derive national means for sources/pathways; state of validation of exposure models; trends in environmental/body burden levels; TEFs/TEQs; impact of human data on hazard and risk characterization; significance of enzyme induction and other biochemical effects; and the relative roles of data, scientific inference, and science policy in informing regulatory decisions. The Agency plans to address comments provided by the general scientific community, the public, and the Agency's SAB. The current schedule, including revision and additional peer review, should allow completion of the dioxin reassessment by September, 1996.

While the science of the reassessment is undergoing further peer review, EPA will be examining the reassessment's policy implications to determine what changes, if any, are needed in existing programs. While regulatory impact assessments are carried out on every regulation that might be issued, no estimates of the economic impact to the public from regulations that may be based on this reassessment have yet been estimated. Throughout the reassessment process EPA has repeatedly stated that existing Agency efforts and programs will not be changed on the basis of this draft reassessment, but they may change significantly after the completion of the report. EPA is committed to developing an Agency-wide strategy for managing dioxin risks, concurrent with completion of the dioxin reassessment. As with the reassessment, we want to provide an opportunity for public input into our policy evaluations. This winter and spring, EPA will hold dioxin policy workshops to explore the policy implications of the reassessment.

EPA

Testimony of George W. Lucier, Ph.D.
Director
Environmental Toxicology Program
National Institute of Environmental Health Sciences
Before the House Committee on Science
Subcommittee on Energy and Environment

December 13, 1995

Good morning, I am Dr. George Lucier, Director of the Environmental Toxicology Program at the National Institute of Environmental Health Sciences (NIEHS), one of 17 institutes at the National Institutes of Health (NIH). I have conducted research at NIEHS for 25 years and have published nearly 200 papers in the peer-reviewed scientific literature. Roughly 1/3 of them address wholly, or in part, health effects of dioxin. My current research on dioxin and related chemicals is attempting to identify and fill knowledge gaps which create uncertainty in risk assessment. These studies are multidisciplinary and attempt to integrate data from experimental systems, human samples and molecular mechanisms of action.

My involvement with EPA's reevaluation of dioxin's risks has spanned nearly four years and has contributed to the preparation of two of the nine chapters constituting the health effects documents. I was the lead author of the "Carcinogenicity" chapter, and I co-chaired the committee with Dr. Mike Gallo (Environmental and Occupational Health Sciences Institute of New Jersey) that prepared Chapter 8 on "Dose Response Evaluations." I also served on a Department of Health and Human Services (DHHS) committee which reviewed a preliminary draft of Chapter 9, the "Risk Characterization" chapter. The Public Health Service has played a key role in evaluating human health consequences from dioxin and in the risk communications part of the reassessment and has worked with EPA on this issue.

General Issues

The purpose of the reevaluation was to use new information on dioxin's mechanism of action to improve estimates of risks at various exposure levels. The centerpiece of the reevaluation reflects the general scientific consensus that most, if not all, of dioxin's effects are mediated by a cellular receptor, which functions in a manner analogous to receptors for steroid hormones. I will come back to this receptor system later in my testimony. I believe that EPA has been extraordinarily thorough in involving the best scientific minds in the reevaluation process as chapter authors, members of peer-review panels for individual chapters, or as ad hoc members of the Science Advisory Board's review of the reevaluation document. It is safe to say that most of the top scientists in the dioxin arena have been involved in one way or another.

The reevaluation of dioxin's risks by EPA represents the most visible effort by a U.S. regulatory agency to move away from default methodologies for estimating human risks and to incorporate all relevant scientific information in the decision process. Clearly, we don't know all that we would like to know about dioxin, and clearly uncertainty will remain in human risk estimates. The use of information on mechanism is a very important step in reducing uncertainty. Efforts such as this one will help restore public confidence in regulatory actions.

I would now like to comment on specific scientific issues within the framework of risk assessment that impact on human health effects of dioxin and related chemicals.

Hazard Identification

Dioxin causes a number of adverse effects in experimental animals and some of those effects have been associated with high dioxin exposures in humans. In regard to cancer, 17 studies have been conducted in rodents and all are positive. Epidemiology studies on humans exposed occupationally or accidentally to dioxin at high doses provide evidence that dioxin is a human carcinogen although the influence of confounding factors cannot be entirely ruled out. Dioxin also produces a number of non-cancer effects in experimental animals such as birth defects, reproductive problems, neurologic disorders, and hormonal alterations, some of which occur at low doses. Recent studies in humans suggest that some non-cancer effects may also occur in humans exposed to high doses. In addition to adverse health effects, numerous studies in the scientific literature demonstrate that dioxin causes a vast array of hormonal, molecular, and biochemical effects some of which are likely involved in the adverse health effects described above. It has been called, with good reason, an environmental hormone or endocrine disrupter. I will come back to dioxin's effects later in my comments on dose-response relationships.

As I mentioned earlier, it is generally accepted by the scientific community that most, if not all, of dioxin's effects require an initial interaction with a cellular protein called the Ah receptor. The Ah receptor, when bound to dioxin, can trigger changes in the function of genes, and it is those changes that most scientists think are an early and necessary event in the ability of dioxin to cause cancer and non-cancer effects. However, our knowledge of the precise way that changes in gene expression lead to toxicity is far from complete. It is this knowledge gap that creates much of the uncertainty in risk estimation at low exposure

levels.

My bottom lines on hazard identification are that dioxin should be considered a probable human carcinogen and that non-cancer effects of dioxin and related compounds are of public health concern.

Exposure Assessment

Dioxins are produced in a number of ways. The key point is that the opportunity for dioxin production and contamination is present whenever heat, chlorine, and organic materials are together. The most notable historical sources of dioxin have been contamination of herbicides (e.g. agent orange), emissions from incinerators, and bleaching of paper although it should be noted that American paper industries have developed and applied new technology to dramatically decrease dioxin emissions during the paper-bleaching process.

Current estimates are that adults in the U.S. are exposed to approximately 10 picograms of the prototypical dioxin, 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) every day. For reference, this amount is equivalent to about 1 trillionth of an ounce. Although this number is very small, dioxin is an extraordinarily toxic chemical. Dioxin exposure comes primarily from consuming contaminated foodstuffs. Current average exposure levels of American adults is 10-20 times higher than the exposure level that EPA estimates could cause up to one cancer in a million people exposed over their lifetimes. EPA and other risk assessors acknowledge that this cancer risk estimate is clearly conservative, and that the actual risk could very well be lower.

It is important to recognize that human risks from dioxin must include an evaluation of

numerous other environmental chemicals that act through the same mechanism as TCDD. For example, there are 75 different dioxins, over 100 different structurally related chlorinated dibenzofurans and some dioxin like polychlorinated biphenyls (PCBS). In addition, brominated analogs of dioxins and furans are environmental contaminants. Toxicity of these chemicals appears to be proportional to the strength of their binding to the Ah receptor and the length of time that the chemical remains in the body. Thus, when appropriate scientific information is available, it is possible to calculate the total exposure to dioxin-like compounds and estimate risks of that exposure. Using this approach, it appears that only 5-10% of our exposure to dioxin-like chemicals is from the prototypical dioxin, TCDD. In other words, the average person is exposed to the equivalence of 100-200pg dioxin per day.

Dioxins are persistent chemicals in the human body and in the environment. For example, the biological half life of dioxin in humans is 7-10 years. This means that if two molecules of dioxin enter your body today, one will be left 7-10 years from now. Dioxin is found preferentially in fat which means that fatty tissues and human milk contain significant amounts of dioxin. Based on human milk concentration data, newborns who breast feed for 6-12 months, receive a dose of dioxin, while nursing, approximately 15 times higher than the average adult in the United States. Although, this exposure level is of concern, the benefits of breast feeding certainly outweigh the risks.

The summary of my comments on human exposure is that human exposure to dioxins is broad-based (everyone has some dioxin in their bodies), and because of its biological persistence, everyone alive today will retain dioxin in their bodies for their lifetimes, even if

their exposure ceased now.

Dose-Response Evaluation

The component of risk assessment that generally creates the most uncertainty is dose-response evaluation, and dioxin is no exception. While there is considerable data to support the claim that dioxin produces adverse health effects in humans, at least at high doses, I believe that there is legitimate scientific debate regarding health effects at lower doses. Data from experimental systems provide evidence that dose-response relationships for dioxin's effects on gene expression are likely linear; that is a proportional relationship appears to exist between exposure level and effect over a wide dose range. Therefore, it is fairly straightforward to estimate the magnitude of these kinds of responses outside the range of observable data. If we were confident that health effects caused by dioxin exhibited the same dose-response relationships as changes in gene expression, then risk assessment would be easy. A linear model would estimate risk with reasonable certainty. However, this is not the case. Our laboratory and others have shown that dose-response relationships for complex responses such as disease are different than those for changes in gene expression. We are conducting research to better understand the molecular and biological determinants of dose response, but we do not yet have the answer. Neither linear models nor threshold models (assume that there is an exposure level below which no effect occurs) are based on a solid scientific base. What is needed is the development of credible biologically-based models for estimating health risks from exposure levels encountered from day-to-day living. This effort should work towards such models for both cancer and non-cancer effects since it could be that adverse outcomes such as reproductive toxicity occur at lower exposure levels

than cancer.

Relevance of Animal Models for Estimating Human Risks

There has been considerable debate regarding the relevance of rodent data in estimating human risks. I believe that there is convincing evidence to support the use of rodent data. First, rat or mouse cells, like human cells, contain the Ah receptor which, as discussed earlier, appears essential for dioxin responses. Second, the amount of dioxin-like chemicals required to elicit changes in gene expression is approximately the same in both rats and humans. The human data has been obtained from people who were occupationally or accidentally exposed to dioxin. Third, the spectrum of toxic responses caused by dioxin in rats is similar to the spectrum of toxic effects associated with dioxin exposure in humans including cancer and reproductive parameters. The problem is that we don't have adequate data to determine low-dose adverse effects in rats although good data on molecular effects is available. I am reasonably confident, however, that the rat is an appropriate model for estimating human risks with one exception; that is, rodents clear dioxin from their bodies much more rapidly than observed in people. The half-life of dioxin in rats is 25 days compared to 7-10 years in people. This means that the chronic exposure level which produces a given body burden of dioxin in humans is approximately 100 times lower than that needed to produce the same tissue burden in rats. Conversely, if rats and humans each had the same daily intake of dioxin for two years, humans would have 100 times more dioxin in their bodies than would rats. This needs to be factored in when using rodent data to estimate human risks.

Summary

EPA has asked for and received considerable input from the scientific community in their reevaluation of dioxin's risk. Taken together, information on human exposures and health effects, experimental studies and levels of environmental contamination provide evidence that we should be concerned about current levels of human exposure to dioxin and dioxin-like chemicals. EPA's risk characterization, I believe, is correct in expressing that concern. This conclusion is supported by information present in the background chapters which were peer-reviewed in 1992 and 1993. However, this statement does not mean that adverse health effects have been shown to occur as a consequence of current exposures of the general population in the United States. The risk characterization does suffer from the need to condense 2000 pages of background into a 50 page characterization. The selection of supporting information may have caused some of the concerns expressed by the Science Advisory Board. This ongoing review when completed should improve the risk characterization chapter. Finally, EPA's reevaluation of dioxin's risks has been and remains a daunting task. EPA should be commended for conducting an extraordinary open and scientifically-based assessment.

House Hearing 13 Dec 95

The following points are worth serious consideration in the Hearing on Dec 13:

1) EPA has never before conducted an assessment with as much input from outside scientists and reviewers. Beginning in 1991, EPA has held public meetings, public scientific reviews with industry and environmental scientists on every panel. Throughout the process, EPA met with industry scientists and representatives and conducted fora and meetings.

Question: Did industry representatives want to dictate the language of every part of every chapter, including the results of the scientific experiments?

Question: Has EPA ever conducted a scientific assessment with this much input and review from outside scientists?

2) For the past five years or longer, the scientific literature has expanded on our knowledge and understanding of the toxic effects of dioxin and related compounds. All research results have confirmed that these chemicals are toxic OR expanded on the health effects caused by these chemicals. New understanding of the way these chemicals work only serves to confirm that the entire group of compounds poses a health threat.

Question: Have any scientific inquiries in recent years revealed that dioxin or related chemicals are NOT toxic?
Question: Isn't it true that EVERY experiment on cancer in lab animals has revealed that dioxin causes cancer?
Question: Isn't it true that the mechanism by which dioxin acts is found in humans, lab animals and wildlife?

3) Since 1990, the most dramatic finding from scientific research has been that singe doses of dioxin given to lab animals can cause serious problems with the reproductive system of animals. This work was originally reported at the now famous Banbury conference in the fall of 1990 by researchers from the University of Wisconsin at Madison.

Question: Can dioxin affect the reproductive systems of animals at low doses? At levels people are NOW exposed to?
Question: Are these effects reversible? That is, will the reproductive problems go away later in life?

4) EPA and the other federal agencies have some experience with controlling toxic chemicals that have some of the same problems seen with dioxin: wide spread exposure, higher levels of exposure than believed, low dose effects and subtle (not lethal) effects. The best model for this is lead, in which millions of US children now suffer from poisoning and resultant permanent impairment.

Question: What experience does EPA have with controlling

chemicals that are wide spread, low level poisons that are above the "margin of safety"?

Question: Does EPA's policy on lead, in which ALL exposures are recognized as health threats, offer any precedent for dealing with dioxin?

Question: Should not EPA move rapidly to incorporate this work into an aggressive program to identify and eliminate dioxin sources?

5) This reassessment is the largest, most comprehensive, involving the public and scientific communities more than in ANY OTHER EPA activity. EPA still is adding new literature, research findings and is now adding still more perspectives in redrafting the final two chapters.

STATEMENT: EPA is to be commended for carrying out a thorough review that included the scientific community and the most up to date information available from the best research labs in the US and the world.