

**Comments Offered to the
Committee To
“Review EPA’s Assessment of the Health Implications of
Exposure to Dioxin”**

**Board on Environmental Studies and Toxicology
National Academy of Sciences
Washington, DC**

22 November 2004

by

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Summary

- The EPA Draft Reassessment conclusions of cancer risk and non-cancer hazard in the general population are discordant with the results of recent assessments by several international scientific panels. We urge the panel to consider whether this discordance is the result of the compounding of conservative assumptions and approaches adopted in the Draft Reassessment for hazard assessment.

Hazard Assessment Considerations

- The mode of action by which TCDD induces cancer and other responses in laboratory animals has been shown to follow a receptor-mediated, multi-step pathway, and not a one-hit genotoxic process as implied in the draft Reassessment by the selection of a linear, no-threshold cancer dose-response approach.
- While the draft states that the occupational epidemiology findings demonstrate that TCDD is a pan-carcinogen in humans, the systematic and objective application of well accepted causation criteria leads to the opposite conclusion as evidenced by (a) the lack of specific response, (b) low observed response level, (c) multiple confounding exposures, and (d) high uncertainty in exposure estimates, all of which mitigate against concluding that these studies collectively demonstrate a causal relationship.
- Assorted unvalidated risk assessment methods have been adopted in the draft dioxin Reassessment. These approaches do not appear consistent with all of the evidence and the accretive effect of the multiple methodology changes may have led to an overstatement of the degree of non-cancer risk from dioxin.

Exposure Assessment Considerations

- Dioxin emission and exposure controls have been exceptionally effective. General population body levels of dioxin have been dropping steadily for the past 20 to 30 years. The Draft Reassessment evaluation of current exposure levels is based on data that are nearly a decade out of date. Based on current data from the CDC, USDA, and FDA and not included in the Draft Reassessment:
 - Dioxin body burdens in persons of all ages in the U.S. continue to decline and are several-fold lower now than at any time in the past 30 years, and current dietary intake is approximately an *order of magnitude lower* than 20 years ago.
 - For young adults of reproductive age, levels are now approximately *15-fold lower* than levels in persons of the same age in the early 1970s, and approximately one-fourth of the levels used in the Draft Reassessment to represent general population exposures.

Comments of C.T. “Kip” Howlett, Jr.

I am Kip Howlett, Executive Director of the Chlorine Chemistry Council, and I would like to present for your consideration a number of concerns expressed by our members. The Draft Reassessment before you has been commended to this panel for review for many reasons, but chief among these reasons is that the conclusions of this document are at odds with the considered scientific assessments of much of the international scientific community. For example, the EPA Draft Dioxin Reassessment concludes that the cancer risk of background exposures to dioxin may exceed 1 in 1,000 and that current background exposures to dioxin may exceed safe exposure levels, perhaps by more than a factor of 10, for non-cancer endpoints. In contrast, numerous recent international assessments, including those by the European Commission, the World Health Organization, and the United Kingdom, have concluded that the current dioxin background exposure level in the U.S. is generally safe, with no attendant cancer risk.

The charge questions to the panel cover all of the critical scientific issues for evaluating the EPA Reassessment. However, panel members must delve into the complex underlying scientific information related to each charge question. The EPA Reassessment document, and in particular the Risk Characterization Chapter, does not provide sufficient information to critically evaluate all of the scientific issues that are relevant to EPA’s risk characterizations. We strongly recommend that the panel seek out opinions and information on how the EPA has arrived at their risk characterizations and how the EPA document has evolved from a scientific analysis to a highly conservative and controversial policy position.

As you evaluate each charge question, focusing in particular on the magnitude and DIRECTION of the uncertainties in the assumptions adopted in the Reassessment, we urge that you work toward answering this question:

Is the discordance with international scientific evaluations due to out of date exposure information and numerous conservative assumptions in hazard assessment by EPA, each on the conservative end of the range of possible choices, resulting in overall conclusions that are far more conservative than justified by the underlying scientific data?

I would urge that the panel request sufficient time to fully consider the complex scientific issues underlying this risk assessment and provide a full weight-of-the-evidence assessment of each critical assumption in the EPA Reassessment.

Comments of Robert G. Tardiff, Ph.D., ATS

I am Robert Tardiff, a toxicologist and risk analyst with the *The Sapphire Group*. Today, I am speaking on behalf of the Chlorine Chemistry Council.

The characterization of risks to human health is a complex process, particularly for TCDD and the class of dioxins whose toxic properties have been widely studied by investigators around the world. Indeed, the wealth of mechanistic and descriptive toxicity information poses considerable challenges to all who attempt to evaluate its meaning for the health of those individuals exposed systemically to TCDD and its congeners. I am confident that this complexity and magnitude has not escaped the members of this committee as it prepares for its deliberations.

My purpose in addressing you today is to focus your attention on a few select scientific issues that, I believe, warrant your close scrutiny during the coming months. Time today permits only the mention of major topics and raises questions central to your determination of the scientific rigor of USEPA's Draft "Assessment of the Health Implications of Exposure to Dioxins." More detailed expositions of these and other scientific considerations will be shared with you in due course.

The handful of topics that I urge you to focus on are central in the risk assessment paradigm as defined by another NAS Committee some 21 years ago. These topics fall within the *Dose-Response* portion of the four-part risk assessment process, and are vital to assure rigorous and defensible conclusions about human health risks that are expressed within a *Risk Characterization* section.

The issues remanded to you for detailed consideration are divided into the risk of cancer and that of other forms of pathology and dysfunction.

1. Considerations in Estimating Cancer Risks from TCDD and Other Dioxins

In judging the nature and magnitude of cancer risk to humans exposed to assorted congeners of dioxin, the USEPA draft concludes that the dose-response relationship is best defined by a linear, no-biological-threshold categorization.

In your deliberations, consider in depth the merits of such an inference given the substantial weight-of-evidence for modes of carcinogenic activity indicative of genuine biological thresholds and not merely limitations of experimental detection. As a vital corollary, I urge the panel to extend its evaluation and express its collective judgment as to whether a biological

threshold region can also be substantiated confidently for humans exposed to this class of substances.

To facilitate your analysis, the following observations are noteworthy:

1. **MODE OF ACTION:** The mode of action by which TCDD induces cancer and other responses in laboratory animals has been shown to follow a receptor-mediated, multi-step pathway, and not a one-hit genotoxic process. While the draft document acknowledges this mode of action via its adoption of a Hill model for dose-response structuring, the draft subsequently sets aside the non-linear relationship by adopting linear extrapolation to estimate cancer risk in the much lower dose range experienced by humans. One need only return to the reliable and well-recognized principles in pharmacology to realize (a) that substances acting via receptor-modulation have a threshold region in humans, even for potent pharmacological agents, and (b) that the same type of receptor-mediated mode of action for TCDD should lead unquestionably to the same recognition of a biological threshold — thereby meriting the use of a non-linear low-dose extrapolation procedure for TCDD.

Specifically, rat liver carcinogenesis and tumor promotion studies have shown a clear no-adverse-effect level, and histopathological evidence supports a conclusion that tumors do not occur in the absence of frank hepato-pathology. The rat liver tumors represent a complex, non-linear response that is hormonally dependent and likely not active at low exposure levels.

Compelling insights into the non-linear mode of carcinogenic action for TCDD (alone as well as with two PCB congeners) were released recently by NTP in its report of high-quality bioassays for TCDD and related compounds. These observations greatly elevate confidence in the non-linearity of the dose-response relationship. The absence of this information from the draft risk re-assessment clearly calls into question the validity of the draft's reliance on a linear, no-threshold hypothesis. These recent comprehensive findings deserve your careful evaluation for their qualitative and quantitative value.

Also, as a corollary, the selection of the appropriate dose metric requires close examination. Although the draft has specified that cancer risk should be estimated on a body burden basis and has attempted extrapolation to other congeners not only on a body burden basis but also using “toxic equivalency factors” (TEFs), a variety of findings — including those from the NTP bioassay — suggest a far more defensible metric (notably, intake) and mixture approach that can certainly be tested with the more recent bioassay data.

2. **EPIDEMIOLOGY FINDINGS:** Human epidemiology studies related to dioxin should not be overlooked. Admittedly, their design and execution are limited

and highly confounded, characteristics commonly present in studies of exposures in the ambient environment; however, these dioxin-related studies must be interpreted in terms of well-recognized epidemiologic approaches. For instance, while the draft states that the occupational epidemiology findings demonstrate that TCDD is a pan-carcinogen in humans, the systematic and objective application of well accepted causation criteria first articulated by Sir Bradford Hill leads one to the opposite conclusion as evidenced by (a) the lack of specific response, (b) low observed response level, (c) multiple confounding exposures, and (d) high uncertainty in exposure estimates, all of which mitigate against concluding that these studies collectively support a causal relationship.

Furthermore, the draft's assertion on this matter is discordant with the findings in laboratory animals which show no pan-carcinogenic activity and only highly organ-specific responses at doses that far exceed those encountered by humans. .

The value of epidemiology studies can be enhanced, at times greatly, by the introduction of human elimination kinetics into the quantitative dose-response assessment for cancer potency. This would be possible for TCDD. Regrettably, the draft has not sought to apply such an approach to estimating risk. I urge the Panel to evaluate the application of recent kinetic modeling by numerous scientists on the magnitude and direction of the cancer risk estimates based on the human data. One can only wonder whether this recent understanding relying on human data might render the draft Reassessment's estimates of cancer risk either more or less reliable.

As a final note, the draft Reassessment presents cancer dose-response characteristics based on epidemiological studies in which the SMRs range from 1 to less than 2.0 for total cancer mortality, SMRs arguably in the range of noise in most epidemiological studies. From experience, such an application seems to exceed the limits of the data. "Does this novel approach have the requisite robustness and validated basis for use in quantitative risk estimation for low background exposure levels?" is a question that the panel should consider during the course of its deliberations.

2. Considerations in Estimating Risks of Non-cancer Toxicity from TCDD and Other Dioxins

In judging the nature and magnitude of non-cancer risk to humans exposed to assorted congeners of dioxin, the USEPA draft has adopted non-traditional and scientifically questionable procedures to characterize the dose-response relationships for dioxin.

In your deliberations, consider in depth the merits of the unvalidated methodological changes introduced in the draft dioxin Reassessment. As a

corollary, I urge the panel to extend its evaluation and express its collective judgment as to whether the risk characterization conclusions in the draft are adequately supported by the all of the evidence and whether the accretive effect of the multiple methodology changes may have led to an overstatement of the degree of non-cancer risk from dioxin.

To facilitate your analysis, the following observations are noteworthy:

1. **BASES FOR IDENTIFYING ADVERSE RESPONSES AND IMPACT ON MARGIN OF EXPOSURE ESTIMATES**: Long-established practices in non-cancer risk assessment have defined histopathological changes as candidates as cornerstone evidence for defining tissue changes as adverse to the health of exposed organism.. These practices have, with a few exceptions (e.g., acetylcholinesterase inhibition), relied on biochemical changes as supportive evidence of the presence or absence of decrements in organ functions. This draft Reassessment appears a notable exception in as much as it aggregates both histopathologic lesions with biochemical changes with no attempt to identify inter-dependencies. As such, the approach in the draft lacks acknowledgment of the presence of defense mechanisms and redefines, with no demonstrable basis, biochemical changes in the absence of direct pathological evidence as an index of injury. The outcome of this change in practice is the introduction of non-science-based judgments leading to larger estimates of risk (that is, smaller margins of exposure) than would be justified from a rigorous application of a weight-of-evidence analysis. The Panel should consider rendering its collective judgment on the suitability and merit of such changes in approach.
2. **BENCHMARK DOSE MODELING**: The draft Reassessment describes the use of benchmark dose (BMD) modeling, a procedure accepted by the Agency as a legitimate tool for low-dose estimates of risks as noted in its widely disseminated risk assessment guidelines. A prominent feature of this approach is the modeling of data to specified incidence level, namely the 5% rate of response (also described as the "ED05"). That stopping point was based on the robustness of the values at that incidence level and the realization of the instability of estimates at much lower levels. The dioxin draft, however, describes the BMD stopping point as the ED01 or the one percent response level, yet the dioxin data provide no basis for arguing that the ED01 is as robust as the ED05. Here also, a methodological change leads to a lowering of the margin of exposure, creating the impression that the estimated risks are higher than justified by the data. Perhaps the panel would examine the accretive impact of this and similar departures from science-based methods, particularly for continuous data.
3. **DOSE METRIC**: The draft also relies on body burden-based dose-response assessment for non-cancer toxicity. This poses a dilemma since data underlying key sensitive responses are based on acute administration of TCDD, whereas

actual human exposures are chronic and consist of variable mixtures of congeners, with more than 90% of mixture attributed to congeners other than TCDD. Consequently, I urge the committee to carefully consider and render its judgment on two issues:

- a. Can responses observed in acute-dose studies be directly extrapolated to chronic body burdens? The recent evaluation of the World Health Organization (WHO) Joint Expert Committee on Food Additives Monograph on dioxins should be highly informative to the committee's deliberations.
- b. Can current TEFs be used for risk assessment for mixtures on a body burden basis? The current WHO TEF procedure is specified for *intake*-based assessments. Furthermore, numerous studies from EPA's own laboratories have demonstrated that under the real-world situation of *chronic* exposures to mixtures, the current TEF system does not reliably predict responses on a *body burden basis* due to large differences in distribution and elimination kinetics among congeners. "Is the body burden approach to risk assessment for the real-world exposure situation using current, intake-based TEFs for these compounds appropriate?" is a question that the panel is encouraged to address by examining in part the findings of the NTP bioassays.

That concludes my remarks. Thank you for your attention. I wish the Committee the greatest success in meeting its charge.

Comments of Lesa L. Aylward, M.S.

I am Lesa Aylward of Exponent, a scientific and engineering consulting firm. I have experience in the assessment of risks of dioxin in a variety of contexts and have published in the areas of exposure assessment and kinetics for dioxins. I appreciate the opportunity to submit comments to your panel, and am commenting on behalf of the Chlorine Chemistry Council.

A key concept discussed in the Reassessment document is “Margin of Exposure”, or MOE. This is defined as a ratio between a “point of departure”, representing a NOAEL or LOAEL, and an exposure level; in this case, the EPA’s evaluation of “current” exposures. The Reassessment document concludes that the current MOE for the general population is insufficient.

Dr. Tardiff has highlighted a few of the novel approaches in the hazard assessment presented by EPA that might result in an estimate of point of departure or hazard that is unduly conservative. I would like to address the exposure side of the MOE assessment.

When the EPA Science Advisory Board reviewed the Reassessment in 2000, they noted the lack of robust databases on current exposure to dioxins in the U.S. Since that time, several U.S. agencies, including the USDA, the FDA, and the CDC have expended considerable resources to develop updated exposure information. These data are not included in the Reassessment document before you.

In addition, the USEPA has completed a new inventory of dioxin emissions for the year 2001, a follow-up to the inventories for 1987 and 1995. However, the results of the 2001 inventory have not been publicly released and are also not included in the document before you.

Because the dioxin exposure situation is highly dynamic, I’d like to highlight some of the findings from the new USDA, FDA, and CDC data sets and place these findings in an historical context. In addition, I urge you to invite representatives from these agencies to present these data sets to you in more detail, as they are critical to evaluating fully the conclusions of the Reassessment.

USDA Data. The USDA, in cooperation with the FDA and the USEPA, first conducted statistically based sampling of beef, pork, and poultry products in the mid-1990s. The current USDA sampling effort during 2002 and 2003 shows declines in dioxin levels from the mid-1990s levels in these products ranging from 30 to 80%, or approximately a factor of 2 (for a preliminary report, see Huwe et al. 2004).

The FDA has been phasing in dioxin analyses into the Total Diet Study. This summer FDA announced dietary intake estimates for dioxins and furans based on food sampling

conducted in 2001 and 2002 (see <http://www.cfsan.fda.gov/~lrd/dioxee.html>). The dioxin and furan intake estimates for adults presented by the FDA are approximately two-fold lower than the dietary intake estimates presented in the Reassessment document based on mid-1990s sampling data, a decrease consistent with the USDA data.

The CDC has been actively engaged in developing data on the levels of dioxins in the bodies of persons in the U.S. general population. These efforts include at least two separate initiatives: analysis of blood samples taken during the National Health and Nutrition Examination Survey program, and analysis of blood samples taken from selected general population groups around the U.S. serving as control populations for studies of potentially exposed groups. The results of the latter effort were presented this summer in a public meeting and contain estimates specific to different age groups (Patterson et al. 2004). I would like to highlight some of the results of these data in the context of earlier sampling efforts for the U.S. population.

Figure 1 shows the trend over the past 30 years in measured serum dioxin levels for persons born during different time periods (data from Kang et al. 1990; Graham et al. 1986; Stanley and Orban 1991; and Patterson et al. 2004). The data are sporadic, but the most complete data are for persons born between about 1935 and 1955. For this group, current body burdens are now about 4-fold lower than in the early 1970s. Because of the very slow elimination of dioxins, this implies a much greater than 4-fold decrease in exposures during this time period (Aylward and Hays 2002; Lorber 2002). Dietary intake estimates from the US and Western European countries show approximately 10-fold declines in dietary dioxin and furan intakes over the most recent 20 years, supporting the trends in serum levels of dioxins (dietary intake estimate data from USEPA 2003; Liem et al. 2000; UKFSA 2003; USFDA 2004; and Furst and Wilmers 1997). The body burden data suggest that declines in intakes began in the 1970s (see also Winters et al. 1998).

The dramatic decline in exposure is most evident in Figure 2, which presents data for persons in the age range of 15 to about 35 years of age at each time point. The blood levels observed in this age group at each time period have declined by nearly *15-fold* during the past 30 years. This age group, which includes persons of current and near-future reproductive age, is of particular interest in the context of EPA's Reassessment because of the focus on a potential for adverse effects on children born to mothers with dioxin body burdens. The blood levels in persons of reproductive age are four-fold lower than the levels used in the Reassessment to assess MOE (EPA estimates average serum lipid TEQ at 25 ppt), and are already *lower* than the levels predicted in the Reassessment for the year 2030.

I urge the panel to obtain detailed information on the current data from scientists at the USDA, FDA, and CDC, and to ask the USEPA for detail on the dioxin emissions inventory results for 2001. This body of data on current exposure should be viewed in an historical context in your evaluation of the Reassessment. These data indicate that,

whatever the point of departure for hazard assessment selected by EPA, the current margin of exposure in the populations of greatest concern (adults of reproductive age) is approximately 4 times greater than estimated by EPA, and the current MOE is more than 10-fold greater than existed 25 to 30 years ago. Most importantly, current exposure trends continue downward.

This historical context is critical to the evaluation of the EPA Reassessment conclusion that current background exposures are too high and the current margin of exposure is too low. I would urge the panel to consider this question:

Do these data, indicating that exposures and body burdens in young adults are more than ten-fold lower than 30 years ago, suggest that the EPA conclusions of hazard and risk at current background exposures are overly conservative?

Thank you for the opportunity to present these comments.

References for Exposure Comments

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Figure 1: Temporal trends in A) Mean measured lipid-adjusted levels of dioxins and furans in persons in the U.S. general population from different birth cohorts, and B) estimates of dietary intake of PCDD/Fs. Note that the serum lipid data for year 2000 include TEQ contributions from “dioxin-like” PCBs, while the earlier time points include only dioxin and furan congeners.

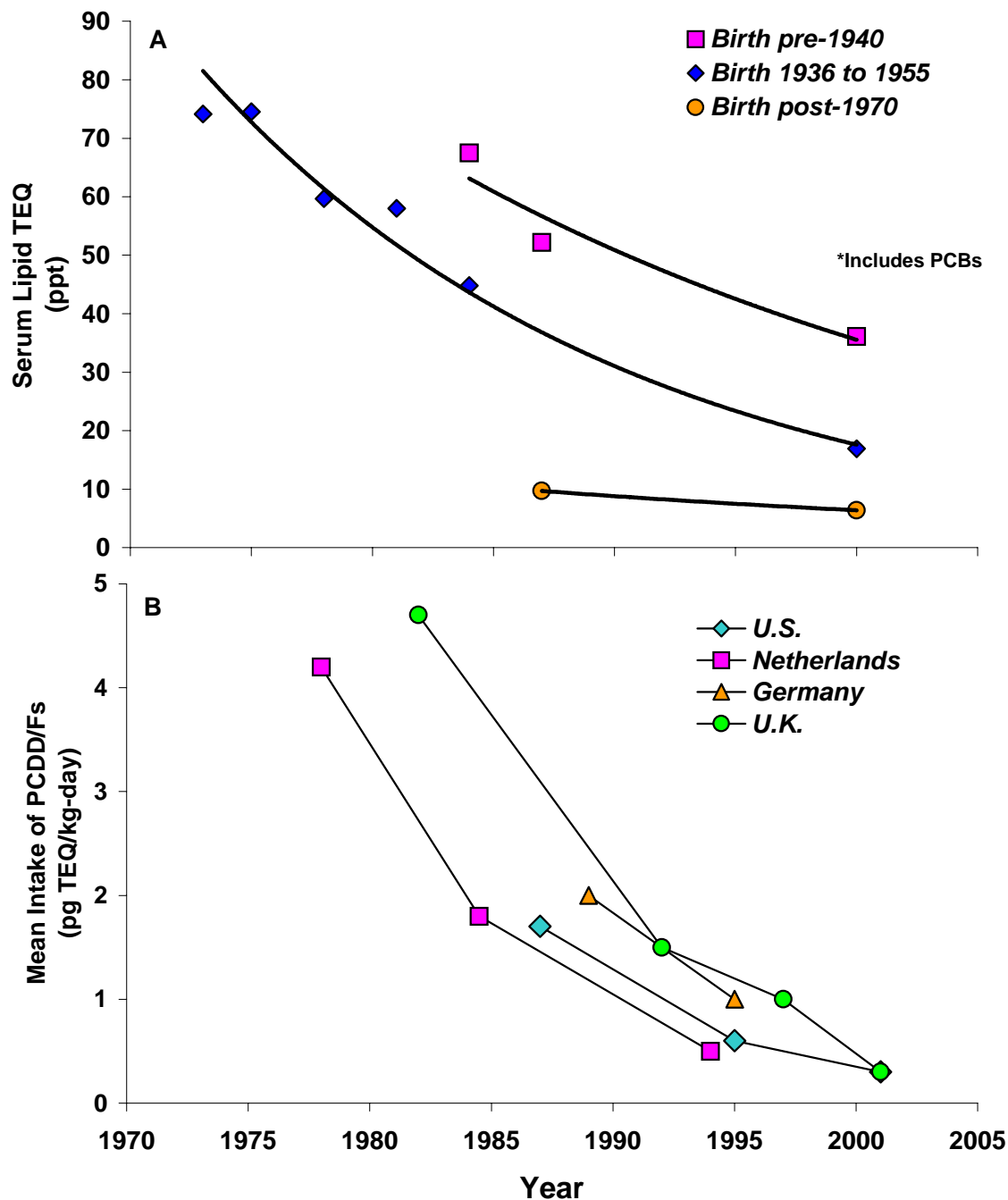


Figure 2: Mean measured levels of dioxins and furans in persons approximately 15 to 35 years of age at different points over time.

