March 26, 2010

NOTE TO: PETER PRUESS

Thank you for the opportunity to participate in the interagency science consultation on the response to the NRC's evaluation of EPA's dioxin reassessment. The document was reviewed by several components of the Department of Health and Human Services, including the Food and Drug Administration, the National Center for Environmental Health/Agency for Toxic Substances Disease Registry, the National Institute of Environmental Health Sciences/National Toxicology Program, the National Institute for Occupational Safety and Health, and the Office of Public Health and Science. Their comments have been consolidated and are attached. Let me know if you have any questions about them. I look forward to hearing about next steps in the reassessment of dioxin.

Sandra Howard
Senior Policy Analyst
Office of Science and Data Policy
U.S. Department of Health
and Human Services

3/26/2010

HHS Comments on
"EPA's Response to 'Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment' Published by the National Research Council of the National Academies"

BACKGROUND

Since 1991, the United States Environmental Protection Agency (EPA) has been working to complete a scientific reassessment of the health risks of exposure to Dioxin-Like Compounds (DLCs). In 2004, EPA sent a 2003 draft document titled "Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds" to the National Academy of Sciences (NAS) for review.

In 2006, the NAS published a report titled "Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment." The NAS report recommended improvement in the quantitative approaches used by EPA to characterize risks. Three areas that were specifically identified are:

(1) Justification of approaches to dose-response modeling for cancer and non-cancer end points,
(2) Transparency and clarity in selection of key data sets for analysis, and
(3) Transparency, thoroughness, and clarity in quantitative uncertainty analysis.

In response to these three areas of concern, EPA drafted a document titled "EPA's Response to 'Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment' Published by the National Research Council of the National Academies."

Following are the compiled comments from five HHS components on this document, hereafter referred to as "the EPA Response" or "the Response". Participating agencies or offices include the Food and Drug Administration (FDA), the National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP), the National Institute for Occupational Safety and Health (NIOSH), the National Center for Environmental Health/Agency for Toxic Substances Disease Registry (NCEH/ATSDR) and the Office of Public Health and Science (OPHS).

COMMENTS

Overarching

Overall, EPA's *Response* is well written, comprehensive in the points it addressed and scientifically robust. The EPA document provides an understandable review of the epidemiological and toxicological literature concerning the potential health hazards

associated with DLCs. Likewise, the Science Plan for developing the *Response* is well designed and articulated.

In their review of the 2003 Reassessment, the NAS also provided a number of recommendations to address key concerns. Each of those recommendations is included on Page 7 of the NAS review. In general, the EPA *Response* to the key NAS Findings considered the recommendations of the NAS.

It would be helpful if there were a better linkage between the previous analyses from the 2003 document to the present *Response* to NAS. Such linkage is lacking particularly for cancer slope factors between the two assessments. For example, in the 2003 document there were several hypothesized precursor events for cancer. These endpoints are discussed in Appendix H as cancer precursors, but are not used in either dose response modeling for cancer or for derivation of an RfD. The reason for this exclusion should be better described. In addition, it is not clear whether this is an extension of the dose response chapter or an entirely different document. This should be clarified.

Transparency/Study Selection

The Ranch Hand cohort results were excluded from the EPA qualitative cancer comparisons due to inability to distinguish between exposures to 2,4,5-T, and its contaminant TCDD, and exposure to 2,4-D, the other herbicide component of Agent Orange, as stated in chapter 2 (2-65). Inability to control for exposure to other chemicals including 2,4-D is a problem of a majority of occupational cohorts included this assessment, most apparently in the NIOSH cohort that included workers from multiple plants. However, TCDD is the main concern, and evidence of carcinogenicity of 2,4-D in humans is sparse. Production data from the Dutch cohorts (Boers et al., 2009) and Hamburg cohorts (Flesch-Janys et al., 1998) illustrate the range of potential exposures among chemical workers. The lack of dose-response, and elevation in "all cancer" mortality in Ranch Hand (Akhtar et al., 2004), should not be a reason for the exclusion of results generated by this cohort from qualitative cancer assessment.

The reasons some studies were excluded for the development of an RfD and cancer slope factor are not clear. Some studies were excluded that appear to be consistent with the inclusion criteria. For example, EPA did not include DEN initiated models or the transgenic models (Wyde et al). These are 26-week bioassays that would provide useful information.

Why was a meta analysis not attempted – for example for CVD or diabetes – by combining some of the industrial cohorts this could be accomplished (see Humblet et al 2009)?

Endpoint Exclusion Criteria

The endpoint exclusion criteria are poorly articulated. In some accepted studies not all endpoints made it into the candidate RfD array and it is not clear why. The relevant

section (4.2.1) is not clear about the distinction between relevant and non-relevant endpoints.

Endpoint Selection in Bioassay

There is an inconsistency in how EPA picked which tumor data to model from the NTP reports. EPA does not use the NTP carcinogenic calls consistently. From the 1982 NTP report, EPA uses statistical significance in choosing the tumor types to model which results in more cancer types than were called in the NTP report. In contrast, for the 2006 NTP report, they do not use uterus, even though, it contributed to the evidence for carcinogenicity and was a tumor site that was statistically significant.

EPA could better describe why they did not use the poly 3 adjustment for early deaths when analyzing the NTP data.

Human Epidemiologic Studies

The description of the epidemiologic studies considered in this evaluation is very thorough and accurate. This level of description is important to ensure transparency in justifying the final studies selected for risk assessment modeling.

The preferred risk assessment model is derived from epidemiologic data, namely, a NIOSH cohort of dioxin-exposed U.S. workers. This seems quite appropriate, given the comprehensive nature of the cohort (e.g., the wide range of exposures and large number of plants contributing information) and the attention given to dose modeling in this cohort. The cancer slope factor is based on the Cheng et al. (2006) reanalysis of dose-response modeling conducted by Steenland et al. (2001). EPA used the all-cancer model lagged 15 years, and removed the highest 5% of exposed persons as a means of minimizing the problem with cancer risk attenuation at high doses. This appears to be an acceptable way of addressing this problem, which is common in occupational epidemiology studies.

Notably, however, there are other approaches that could have been used. For example, a piecewise loglinear model (lagged 15 years) might provide a better fit to the data than deleting the high-dose individuals. Using the estimated risk at the lower ranges of dose (which are most relevant for risk assessment) is straightforward with piecewise models. This is a minor issue, however, as the choice of the most appropriate dose-response model to employ must consider a wide variety of factors in addition to model fit, and EPA may not have had the data necessary to identify the best-fitting model.

Dose-Response

One key area in which the NAS requested a response from EPA was justification of approaches to dose-response modeling for cancer and noncancer endpoints. The following comments focus on that aspect of the EPA dioxin risk assessment, particularly in regard to pharmacokinetic modeling for the NIOSH dioxin cohort.

As noted in the EPA *Response* to NAS, an earlier analysis of the NIOSH dioxin cohort (Steenland et al, 2001) relied on a fixed half-life model of TCDD kinetics. Although such a model was consistent with the observed kinetics of humans exposed to low levels of TCDD, more recent data from Seveso indicate that a fixed half-life model is not consistent with the observations of TCDD kinetics in highly-exposed individuals. The updated EPA risk assessment for dioxin makes use of an analysis by Cheng et al (2006), which used a non-linear model of TCDD kinetics (Aylward et al, 2005a) to estimate the internal doses of the subjects of the NIOSH cohort. The Aylward et al (2005a) model includes concentration-dependent elimination kinetics, which the EPA characterizes as consistent with our current physiological understanding of TCDD kinetics. EPA's decision to use a concentration-dependent model of TCDD kinetics, as a fixed half-life model is incompatible with the observed kinetics of TCDD in highly-exposed individuals.

Throughout most of the EPA *Response*, TCDD kinetics are modeled using the physiologically-based pharmacokinetic model of Emond et al (2006). From the standpoint of internal consistency, it would be desirable to use the Emond model rather than the Aylward model for internal dose estimation for the NIOSH dioxin cohort. However, we are unaware of any such analysis having been published, to date.

Choice to Ignore TEQ in Dose Response Modeling

EPA chose not to include background TEQ in the dose response modeling of either the human or experimental animal data. EPA pointed out the uncertainties of the use of TEQs in these efforts; however, we feel that analyzing the data with TEQ will provide a quantitative estimate of this uncertainty. In addition, it will also provide insight into whether the exclusion of the TEQ in the dose response analysis is a conservative assumption. It is thought that if EPA used the TEQ analysis from the NTP cancer studies in rats, this would support the robustness of their cancer slope factors and the use of the TEQ methodology. We would support dose response modeling of mixture studies that include TCDD and other dioxins. Dose response analysis should not be done on mixtures containing the mono-ortho PCBs and chemicals not part of the WHO TEF methodology.

PBPK Modeling

The *Response* presents a comprehensive and voluminous review of peer-reviewed literature to support the pharmacokinetic/toxicokinetic dose-response modeling approaches it has taken to estimate body burden from 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in human (observational) and non-human (experimental) studies.

EPA agreed with the recommendation of the NAS committee to use biologically-based pharmacokinetic models instead of using a simple one-compartment kinetic model to estimate past exposure to Dioxin-Like Compounds (DLCs) on the basis of more recent serum levels. Specifically, the rationale and scientific justification for the selection and application of the Emond human physiologically-based pharmacokinetic (PBPK) model developed by Emond et al. (2004, 2005, 2006) appears justified. EPA assumed that the

same blood TCDD levels leading to effects in animals would also lead to effects in humans; this seems like a reasonable assumption.

The use of pharmacokinetic models in the development of the RfD and cancer slope factors is a clear advance and is supported by the data indicating large differences in the PK between humans and animals and the clear non-linearity in the pharmacokinetics. The uncertainty in the use of these models is well described qualitatively. There are some minor suggestions on the use of these models.

The comparison between the Emond PBPK model and the CADM model are done at dose levels that would either kill the animals or are at least a 1000 times higher than human background. Model comparisons for humans should be at dose levels within the exposure range of interest (0.1-100 pg/kg/d) and the animal dose levels should be at 0.1-100 ng/kg/d.

Using the CADM model to estimate cancer risk from the human epidemiology studies is a significant advance from previous analyses of this data, it would be helpful to examine the same data using the Emond model to better understand the uncertainty in the use of the CADM model.

Non-Cancer Effects

Per the advice of the NAS, EPA calculated a reference dose (RfD) for TCDD. A reference dose is an estimate (with uncertainty spanning about an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of harmful effects during a lifetime. The decision to use this approach seems reasonable and as explained below is aligned with how DLCs are managed in foods internationally.

The EPA document provides an understandable basis for EPA's determination of hazard identification and dose-response analysis. EPA's selection of human studies (Baccarelli et al. 2008, Mocarelli et al. 2008) for derivation of the draft TCDD Reference Dose (RfD) appears to be appropriate, as these studies represent exposures over different life stages including gestation, childhood, and young adulthood. Hence, use of these data to assess the potential risk from exposure to TCDD and other dioxin-like compounds would be relevant to vulnerable members of the population, such as children, pregnant and nursing women, and fetuses. Moreover, use of epidemiology studies decreases the uncertainties that are associated with extrapolating toxicity from animals to humans.

The Baccarelli and Mocarelli studies evaluated health endpoints from people in the Seveso cohort, whose members were exposed in 1976 to high peak concentrations of TCDD, a potent DLC with a TEF of 1.0, as a consequence of an industrial accident in Seveso, Italy. This incident resulted in the highest known exposure TCDD in residential populations. While this approach complicated the estimation of average daily doses associated with specific endpoints, EPA was able to calculate candidate points of departure (PODs) for derivation of an RfD from each of the studies. Given that the

source of the exposure to TCDD was an industrial accident, it is possible that other DLCs also were present. Also, it is possible that non-DLC exposures could have resulted from exposure to emissions from the accident; this is possibly a source of uncertainty in these studies. One limitation to this approach is that, in human populations it is not possible to identify a No Adverse Effect Level (or NOAEL) since the reference groups in human studies have background exposures to DLCs. A second limitation is that both of these study populations are small and fairly homogeneous. EPA addressed these latter two uncertainties via application of "uncertainty factors (UFs)", a UF of 10 to account for the lack of a NOAEL and a UF of 3 to account for human interindividual variability that might be unobserved in a small study, for a total composite UF of 30.

With regard to the Mocarelli study, men who had been exposed to elevated TCDD levels when they were children between the ages of one and nine had reduced semen quality 22 years later. From this study, it is difficult to be certain about the relevant time interval over which TCDD dose should be considered. Investigators measured TCDD lipid-adjusted serum concentrations within approximately one year of the initial exposure event. Because effects were only observed in men who were under 10 years of age at the time of exposure, EPA has assumed a maximum 10-year critical exposure window for elicitation of these effects. However, because dioxins are stored in fat tissue and slowly released over many years, it is difficult to be certain whether the observed effects are a consequence of the initial high exposure between one and nine years of age or a function of the cumulative exposure that would have occurred during the entire 22 years between exposure and semen studies, or something in between. The differences between these two dose estimates (the initial high exposure versus the cumulative exposure for the 9 year window) is within an order of magnitude, which is not considered to be a large difference in this context. The RfD derived from the Mocarelli study was 0.7 pg/kg/day.

For the Baccarelli study, on the other hand, both the TCDD and the endpoint (thyrotropin or thyroid-stimulating hormone) levels were measured in neonatal plasma so that there is not uncertainty about the relevant exposure window. Despite these differences in exposure measurement and endpoint, the RfD derived from the Baccarelli study was similar to the one for the Mocarelli study, 0.8 pg/kg/day. Rather than present a single RfD EPA could have presented the RfD as a range between these two very close estimates. Of note is that RfDs that would have been derived from animal studies are higher or lower and mostly within an order of magnitude of these RfDs, so that the data are fairly consistent.

Although different approaches have been taken, EPA's Draft Reference Dose (RfD) for TCDD (0.7 pg/kg-day) is slightly lower than, but similar to, the WHO Tolerable Daily Intake (TDI) (1 – 4 pg/kg-day), the ATSDR Maximum Residue Limit (MRL) (1 pg/kg-day) and the JECFA Provisional Tolerable Monthly Intake (PTMI) (~2.3 pg/kg-day). Although these dose guidelines have different names, the methods for computing them and their interpretations are very similar. Thus, despite the uncertainties that are inherent in trying to draw conclusions from these kinds of data, and that the EPA assessment is more recent, these estimates are close together.

Carcinogenicity

The weight of evidence for TCDD carcinogenic hazard potential is objectively analyzed in the EPA document. For the cancer dose response assessment, EPA derived an Oral Slope Factor (OSF). This approach seems to be appropriate and reasonable. EPA selected Cheng et al. (2006) as the study from which to derive the OSF and the methods used also appear to be appropriate. Considering the possibility that key events in the modes of action (MOA) for TCDD may interact to affect multiple pathways leading to carcinogenesis, EPA's consideration of nonlinear as well as a linear cancer dose-response models is reasonable.

Mode of Action for Cancer

In figures 5.4 and 5.5 EPA describes an MOA for some cancers. As presented, it can be implied from the figures that the adenomas and carcinomas are due to cytotoxicity, which is unlikely to be a key event in the hepatocarcinogenic response. This figure also excludes cholangiocarcinoma, which were the main hepatocarcinogenic event. Recommendation: Since we do not know MOA beyond Ah receptor activation, it may be better to exclude the proposed MOAs in this section.

Cancer Slope Factor

Agreement in RfDs from 2 human studies is encouraging, as is fact that the OSFs from animal [3.2 × 105 to 9.4 × 106 (per mg/kg-day)] and human data [3.75 × 105 to 2.5 × 106 (per mg/kg-day).] fall within a small range. If anything, the humans may be MORE sensitive than the animals.

It would be helpful to present the distribution of cancer slope factors in a figure similar to the Candidate RfD array.

While EPA considered the Seveso cancer study of Warner et al (2002) to be less relevant because it was associated with a single high dose exposure, this is the only cohort in which the peak TCDD concentrations is actually measured. The occupational cohorts require assumptions about the peak concentration.

The cited NTP 1982 report says it is from adenomas and carcinomas but they only use the carcinoma data (Table 5-8).

The use of the Kociba study needs clarification. For example, the Kociba data analyzed here appears to have fewer animals than the published Kociba study.

Quality Assurance

Is there an independent QA plan to cross check the data used in the dose response analysis compared to the paper to evaluate the data for transcription errors, as well as taking info from the appendix into the full chapters?

Specific Comments

Pages 2-1: "chloracne is considered a clinical sign of exposure to dioxin."
NOTE: chloracne indicates HIGH dose exposure.

Page 2-196 lines 27: "As discussed above, female Sprague-Dawley rats (81 control; 82 treatment group)"
NOTE: 30 out of the 80 were scheduled sacrifices during the study so that 50 were dosed for the entire study.

Pages 3-5 lines 25-26: "Recent efforts of pharmacokinetic modeling have supported the concentration dependent elimination of TCDD in animals and humans (Aylward et al., 2005b; Emond et al., 2006)."
NOTE: The Andersen models always had inducible metabolism starting in about 1991.

Pages 3-9 lines 19-25: "The redistribution of TCDD tissue levels from liver to fat with increasing time suggests that binding of the chemical in the liver (including via induction of CYP1A2) is an important kinetic consideration at early exposure points with relatively high applied doses. At steady state levels (longer than 35 days, and low applied doses), there seems to be a tendency for TCDD to redistribute to fat tissue."
NOTE: The redistribution from liver to fat is not a steady-state vs. time issue. It is really related to dose and CYP1A2 induction. Following a single exposure, CYP1A2 takes 1-3 days to peak in the liver, at this time concentrations in liver and fat are dynamic and once the peak cYP1A2 is attained, the peak liver:fat ratio is attained. Following a single dose, overtime, tissue concentrations decrease. As liver concentrations decrease so does CYP1A2 induction and liver:fat TCDD concentrations. Thus, high steady-state exposures result in high liver:fat ratios and low steady-state exposure will result in lower liver:fat ratios.

Pages 3-15 lines 1-6: "Bell et al. (2007b) reported that the disposition of TCDD into the fetus shows dose dependency, with a greater proportion of the dose reaching the fetus at lower doses of TCDD. Further, both CYP1A1 and CYP1A2 are highly inducible (~103−fold) in fetal liver, whereas CYP1A2 shows much lower induction (10−fold) in maternal liver. It has been speculated that this is due to the lower basal levels of CYP1A2 in fetal liver, as compared to maternal liver (Bell et al., 2007b)."
NOTE: The greater relative disposition to the fetus at low doses may be that less is bioavailable from the dam at high doses due to greater hepatic sequestration in mom's liver and greater elimination.

Table 4-4: These are the PODs and should be mentioned in this table

Page 429 text box: "NTP (2006), however, found virtually no TCDD in the tissues of untreated animals or in the feed stock. In all of these studies, except the 28-day exposure in Bell et al. (2007a), control animals were gavaged with corn oil vehicle. TCDD concentrations in corn oil were not reported in any of the studies.

NOTE: Note the lack of TCDD in control animals was due to incorrect method- with too high a LOD. In the TEF mixture, we could detect TCDD in controls-we saw 13 pg/g fat at 2 yrs and 8 pg/g in liver. The bigger issue here is background TEQ total

Figure 6-3: **S**tates it is from Hattis 2009. EPA should check this citation. It does not appear correct.

Page 20 R-9 Line 5: Wrong Reference
Correct Reference:
NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD) (CAS NO. 1746-01-6) IN FEMALE HARLAN SPRAGUE-DAWLEY RATS (GAVAGE STUDIES) NATIONAL TOXICOLOGY PROGRAM April 2006 NTP TR 521 NIH Publication No. 06-4468