American
Forest & Paper
Association

July 7, 2010

Office of Environmental Information (OEI) Docket
Mail Code: 2822T
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW.
Washington, DC 20460

Re: EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, Docket ID No. EPA-HQ-ORD-2010-0395

Dear Sir or Madam:

The American Forest & Paper Association (AF&PA) is pleased to submit the comments of Dr. Thomas B. Starr in response to the external review draft document titled: "EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments" (EPA-HQ-ORD-2010-0395), notice of which was provided in the May 21, 2010 Federal Register (75 Fed. Reg. 28610).

AF&PA is the national trade association of the forest products industry, representing pulp, paper, packaging and wood products manufacturers, and forest landowners. Our companies make products essential for everyday life from renewable and recyclable resources that sustain the environment. The forest products industry accounts for approximately 6 percent of the total U.S. manufacturing GDP, putting it on par with the automotive and chemical industries. Industry companies produce about $175 billion in products annually and employ approximately nearly 900,000 people earning $54 billion in annual payroll. The industry is among the top 10 manufacturing sector employers in 48 states. AF&PA has a substantial interest in ensuring that the best scientific data and analyses are brought to bear in establishing health benchmarks for dioxin.

AF&PA requested Dr. Thomas B. Starr, a recognized expert in quantitative dose-response assessment, to review EPA's reanalysis document and to provide independent professional comment. With more than 100 published papers in the area of chemical risk assessment, Dr. Starr is extremely well qualified to provide his expert comment and analysis on dose-response issues relating to dioxin. His comments focus specifically on EPA's latest approaches for deriving cancer risk-specific doses, as well as a Reference Dose (RfD) for dioxin. Dr. Starr's report is attached, and we urge that EPA and members of its SAB panel give them thoughtful consideration in their scientific assessment and deliberations.

If you have any questions about these comments, please contact Laurie Holmes at (202) 463-5174 or by e-mail at Laurie_Holmes@afandpa.org.

Sincerely,

Paul Noe
Vice President for Public Policy

Comments on USEPA's Latest Draft Cancer Risk Assessment Approach For Dioxin-Like Compounds

Prepared for
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Washington DC

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7 July 2010

1. Background

On 21 May 2010, USEPA released its response to key comments and recommendations made by the NAS following its extended review of USEPA's 2003 *Exposure and Human Health Risk Assessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin and Related Compounds*. The NAS review identified three key areas that required additional effort on the part of USEPA: 1) improved transparency and clarity in the selection of key data sets for dose-response analysis, 2) further justification of approaches to dose-response modeling for cancer and noncancer endpoints, and 3) improved transparency, thoroughness, and clarity in quantitative uncertainty analysis.

The present comments are focused on the latest approach that USEPA has taken to assessing potential human cancer risks from exposure to dioxin-like compounds. The Agency has derived risk-specific doses and "equivalent oral slope factors" (Tables ES-1, p liii, and 5-3, p 5-96) that quantify expected lifetime human cancer risks in relation to oral dioxin intake. These factors were derived from an upper 95% confidence bound on one slope factor estimate selected by the Agency from among multiple (10) estimates that were provided in Cheng et al.'s (2006) reanalysis of cancer mortality in the NIOSH cohort. The Cheng et al. reanalysis made use of a concentration- and age-dependent pharmacokinetic model developed by Aylward et al. (2005) (the CADM model) to convert worker exposure score histories previously developed by Piacitelli et al. (2000) into age-specific blood lipid concentration profiles for TCDD. These profiles were then processed into alternative dose-metrics, such as serum lipid concentration and AUC versus age, that would be suitable for quantitative dose-response assessment. While the CADM model had been calibrated and validated against measured serum TCDD concentrations for a subcohort of 172 workers from one of the eight NIOSH cohort plants, USEPA chose instead to utilize a different, uncalibrated pharmacokinetic model, that of Emond et al. (2004, 2005, 2006) to develop its oral slope factors for estimating human cancer risk.

As is documented in the following comments, this latest USEPA approach to dioxin cancer risk assessment: 1) remains seriously deficient in transparency and clarity with respect to the rationale for the Agency's selection of key data sets, 2) lacks a convincing rationale for the Agency's chosen dose-response modeling approach in relation to alternative fully credible approaches, and 3) lacks altogether any quantitative uncertainty analysis, most importantly with regard to a) levels of human TCDD exposure, both measured and simulated, and b) the shape of the true dose-response relationship for cancer mortality, particularly at low exposure levels.

These critical deficiencies can be traced, at least in part, to serious and fundamental limitations of the Emond et al. (2005) PBPK model and the Agency's narrow and shortsighted evaluation of the Cheng et al. (2006) reanalysis of the NIOSH cohort cancer mortality experience. Because the Emond PBPK model was also utilized by USEPA in developing its Reference Dose (RfD) estimates for various noncancer

endpoints, many of the serious shortcomings of the Agency's approach to human cancer risk assessment discussed herein are also directly relevant to the Agency's approach to assessing human noncancer risks.

2. There are serious deficiencies with the dose-dependence of the Emond et al. PBPK model that must be corrected

The first indication that USEPA's selection and use of the Emond et al. PBPK model for low-dose extrapolation purposes is problematic comes from the Agency's equivalent oral slope factors that are provided in Tables ES-1 and 5-3 of the new risk assessment document. Inspection of these tables reveals that the Agency's oral slope factor estimates actually increase by more than a 10-fold factor, from 1.1×10^5 to 1.2×10^6, as the associated risk level is reduced from 10^{-2} to 10^{-6}. This highly unusual behavior cannot be attributed to the underlying cancer mortality dose-response relationship estimated by Cheng et al. (2006), since that simple exponential relationship between risk and cumulative exposure is already essentially linear in cumulative exposure for risk levels at or below 10^{-2}. Indeed, this virtually linear relationship between risk level RL (column 1) and AUC_{RL} (column 2), a measure of cumulative exposure, is clearly apparent in Tables ES-1 and 5-3 over this entire risk range.

The *supralinearity* of risk level versus TCDD intake rate must therefore originate in the underlying relationship between cumulative exposure and intake, which, at least in Tables ES-1 and 5-3, is governed by the Emond et al. PBPK model. Examination of the Agency's description of the Emond et al. model (see especially pp 3-10 and 3-34), as well as the human standard model computer code in Appendix C, reveals that Emond et al. incorporated into their model a supralinear Hill function relationship between the extent of CYP1A2 induction and the concentration of AhR-bound TCDD in the liver. The value of the exponent parameter in this empirical relationship was estimated previously to have a value of 0.6 by Wang et al. (1997), using pharmacokinetic data obtained with female Sprague-Dawley rats exposed to single oral doses of TCDD ranging from 10 ng/kg up to 30,000 ng/kg. However, details of the estimation procedure, and any measure of uncertainty in this parameter, such as a standard error of estimate, are not provided in Wang et al. (1997), or anywhere else, for that matter. It is noteworthy that the *lowest* dose utilized in the Wang et al. (1997) experiments, namely, 10 ng/kg, is over 100 times greater than the largest risk-specific dose presented in Tables ES-1 and 5-3, so significant downward extrapolation from the experimental doses utilized by Wang et al. in estimating the Hill function exponent is required to reach the far lower range of exposure levels described in Tables ES-1 and 5-3.

Wang et al. (1997) reported only a final numerical value of 0.6 for the Hill function exponent, without any estimate of uncertainty, such as a standard error or 90%

confidence interval, and without any accompanying sensitivity analysis. Nevertheless, this value has been utilized consistently by USEPA in all six versions of the Emond model, irrespective of species and gestational status, that are described in the risk assessment document (rat gestational/nongestational, mouse gestational/nongestational, and human gestational/nongestational) versions. Interestingly, Wang et al. (1997) commented that "The Hill coefficient was 0.6, suggesting a nonthreshold phenomenon in the tissue response induced by TCDD." This is actually a marked understatement, because any Hill function exponent that is smaller than unity leads to a *supralinear* dose-response relationship at low doses, i.e., a relationship that has a nonphysical, nonsensical *infinite* slope at zero dose!

Figure 1 illustrates a hypothetical Hill function relationship between two variables, y and x, for which the Hill function exponent is equal to 0.6, as in all versions of the Emond et al. model, and in which the EC50 parameter has been set equal to 1 for simplicity. If all of the data that were used to estimate the parameters of this relationship were collected at doses near or above the relationship's EC50, i.e., near or above 1, then any flatness in the dose-response data above the EC50 relative to what would be predicted by a rectangular hyperbola (a Hill function with exponent = 1, which is linear at low doses) will drive the fitted exponent to values smaller than 1, thus forcing the relationship to become supralinear, i.e, forcing it to have a nonphysical, nonsensical, infinite slope at zero dose. This phenomenon can be succinctly described as "the high dose tail wagging the low dose dog", and it has no predictive value whatsoever at low doses! The values that are predicted at low doses are just artifactually constrained by the supralinear shape of the Hill function, which is imposed by the data at far higher doses! Because there are no data in the low dose region, i.e., well below the EC50, there is no counterbalancing force that would keep the Hill exponent value at or greater than 1.

There is a critical need to examine very carefully just how sensitive the risk-specific dose estimates of Tables ES-1 and 5-3 and the candidate RfDs of Figure ES-5 are to the Hill function parameterization of CYP1A2 induction in the Emond et al. PBPK model, because it is CYP1A2 induction that is primarily responsible for the nonlinear relationship between dioxin intake and its concentration in serum and other lipids. The CADM model needs also to be given full and serious consideration, as a credible alternative to the Emond et al. model, for use in estimating risk specific doses and Reference Doses as well. A comprehensive exploration of the low-dose implications of alternative pharmacokinetic models is just one piece of the formal uncertainty analysis that was strongly recommended in the NAS review, but it is, nevertheless, missing from the new assessment. This is not a simple task, and it will require considerable effort on the part of USEPA. However, without such a thorough and critical uncertainty analysis of the Emond et al. and CADM models, the Agency derived risk-specific doses and candidate RfD values will continue to have little or no scientific credibility.

3. Alternative slope-factor estimates from Cheng et al. (2006) must be given full and serious consideration. The substantial residual uncertainty in both exposure and dose-response relationship specification must also be recognized explicitly.

Table 1 reproduces the results of Cox regression modeling of the dose-response relationship between CADM-based TCDD ppt-years and all cancer mortality that were obtained by Cheng et al. (2006) (their Table III). Results from 10 distinct regression analyses are presented, and these are differentiated by the various approaches that were considered in defining the dose metric. Although all 10 analyses utilized some form of cumulative exposure, the analyses differed with regard to whether the exposure metric was untransformed or log-transformed, unlagged or lagged 15 years, complete or excluded the highest 1%, 2.5%, or 5% of exposed person-years.

Two important points need particular emphasis: 1) the NIOSH cohort data are consistent with low dose slope factor estimates that span an enormous range, from *negative* -8.9×10^{-9} per ppt-year (full data, untransformed) to positive *infinite* (log-transformed); and 2) there is little to commend any one particular slope factor estimate over another, despite USEPA's stated preference for the upper 95% confidence bound estimate obtained with untransformed, lagged 15 years, and upper 5% trimmed ppt-years. Of course, after the fact, one can always construct an *ad hoc* rationale to support a particular choice, such as lagging, transforming, and/or trimming, but *a priori*, the simple and straightforward choice of using all the data without lagging, transformation, or any other manipulation is at least as credible as any other choice, and the slope factor estimate resulting from this analysis happens to be negative and statistically insignificant!

A third noteworthy point is that all but the two log-transformed dose-response analyses reported by Cheng et al. (2006) utilized a hazard function that was linear in cumulative exposure, a functional form that is appropriate for genotoxic, direct-acting carcinogens, but is most likely not appropriate for a nongenotoxic, promoting substance such as TCDD (Starr, 2003). More credible dose metrics for promoting substances would include lipid concentration (not AUC), and time spent at or above some threshold lipid concentration. USEPA has argued that linear low-dose extrapolation is appropriate for TCDD because its mode of carcinogenic action remains unknown. However, the weight of evidence strongly supports a nongenotoxic promotional mode of action, and a threshold may well exist for this kind of carcinogenic activity. At the very least, USEPA should implement a threshold-based approach to cancer risk assessment as a credible alternative to the linear low-dose extrapolation it currently favors.

Clearly, an extraordinary amount of residual uncertainty remains regarding the nature of the true dose-response relationship, if any, that may be present in the NIOSH cohort data. USEPA must acknowledge this residual uncertainty explicitly and carry it through into its risk-specific dose estimates. The Agency's use of just a single risk-specific dose for each risk level in Tables ES-1 and 5-3 is very misleading because the large residual uncertainty that remains regarding the true dose-response relationship is not reflected adequately by these single numbers. In fact, this residual uncertainty is not expressed at all! At a minimum, a range of credible, plausible alternative dose estimates needs be provided for each risk level in these tables. A threshold-based approach to the NIOSH cohort cancer mortality data should also be carefully explored.

The residual uncertainty that remains regarding the true dose-response relationship may be attributable in part to exposure misclassification. For example, it has been argued that exposure misclassification may be more severe at high exposure levels, and this will force a flattening out of the apparent response at high doses, thereby weakening (reducing the magnitude of) the overall slope factor estimate (Stayner et al.,1999 and 2003). This is the argument that Steenland et al. (2001) used to rationalize their piece-wise linear and log-transformed dose metrics, and that Cheng et al. (2006) used to rationalize trimming out (excluding) the top 1- 5% most highly exposed person-years from some analyses. There is, however, no convincing evidence pertaining specifically to the NIOSH cohort that supports this speculation regarding greater exposures misclassification at higher doses. In fact, the limited evidence that is available on this question points in the opposite direction.

As was previously discussed, the Aylward et al. (2005) CADM model was used to construct cumulative exposure profiles for each worker in the NIOSH cohort, but prior to doing this, the model was calibrated and validated against serum measurements that had been collected previously for a subcohort of 172 workers from one of the eight NIOSH cohort plants. A comparison of the measured and CADM-modeled serum concentrations for the NIOSH subcohort of 172 workers is presented in Figure 2, reproduced from Figure 4b of Aylward et al. (2005). While the measured and modeled values range over nearly 3 orders of magnitude, the ratio of measured to modeled values rarely exceeds a factor of 10, but this still represents a very substantial amount of residual uncertainty in the CADM exposure estimates. Importantly, however, the discrepancies between measured and CADM-modeled values appear to be no greater at high exposure levels than they are at low levels. In fact, the measured and modeled values appear to be in somewhat better agreement at high than at low exposure values, indicating that exposure misclassification, at least with the CADM modeled values, may actually be less severe, not more, in the NIOSH cohort at high than at low exposure levels. This result casts considerable doubt on the speculation by Steenland et al. (2001) and Cheng et al. (2006) that dioxin exposure misclassification in the NIOSH cohort may have been higher at high than at low cumulative exposure levels.

It is also strongly recommended that the performance of Emond et al. PBPK model be assessed carefully using this very same serum concentration data for the NIOSH cohort. It is noteworthy that when the CADM and Emond et al. models have been evaluated on the same human data sets, the CADM model appears to provide substantially better results. This is illustrated in Figures 3 and 4, which compare the CADM and Emond et al. model predictions with measured serum concentrations for the two acutely exposed patients studied by Geusau et al. (2002). While the CADM model reproduces much of the fine temporal structure that is present in the patient 2 serum concentrations (see Figure 3), this structure is notably absent from the Emond et al. model predictions (see Figure 4). Furthermore, the Emond et al. model appears to markedly overpredict the early serum concentration levels for this same patient (see Figure 4).

4. Summary

We have called attention to serious difficulties with the dose-dependence of the Emond et al. PBPK model. Specifically, the Hill function dependence of CYP1A2 induction upon AhR-bound TCDD has a non-physical, nonsensically infinite slope at zero dose, due to the fact that its exponent parameter has a numerical value smaller than 1, namely 0.6. This leads to artifactual and arbitrarily large increases in the oral slope factors for all cancer mortality that USEPA has provided in Tables ES-1 and 5-3 as the TCDD intake approaches zero. At a minimum, the Emond et al. PBPK model must be subjected to a comprehensive quantitative uncertainty analysis to better determine the low dose implications of the underlying assumptions that have been made in this model about TCDD pharmacokinetics. Absent such a thorough and comprehensive uncertainty analysis, the Agency-derived risk-specific doses and Reference Doses will continue to have little or no scientific credibility. The CADM model must also be seriously considered as a viable and credible alternative to the Emond et al. model that can and should be used to estimate alternative risk-specific doses as well as Reference Doses for noncancer endpoints.

The substantial residual uncertainty in both exposure and dose-response relationship specification for the NIOSH cohort all cancer mortality data must also be recognized explicitly. The Agency must fully consider other credible alternative interpretations of the NIOSH cohort mortality data. In particular, a threshold-based approach to the NIOSH cohort cancer mortality data should be carefully explored because the weight of evidence strongly supports a promotional and possibly thresholded mode of carcinogenic action for TCDD.

Finally, alternative slope-factor estimates that were provided in Cheng et al. (2006) must be given full and serious consideration. At a minimum, a range of credible,

plausible alternative dose estimates needs to be provided for each of the risk levels that are provided in Tables ES-1 and 5-3.

5. References

Full citations are provided below for those references not already cited in the USEPA draft document.

Aylward et al. (2005, 197014).

Cheng et al. (2006, 523122).

Emond et al. (2004, 197315).

Emond et al. (2005, 197317).

Emond et al. (2006, 197316).

Geusau et al. (2002, 594259).

Piacitelli L, Marlow D, Fingerhut M, Steenland K, Sweeney MH (2000). A retrospective job exposure matrix for estimating exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Am J Industrial Med* 38(1):28-39.

Starr TB (2003, 594271).

Stayner et al. (1999, 198654).

Stayner et al. (2003, 054922).

Steenland et al. (2001, 197433).

Wang et al. (1977, 104657).

Table 1. Summary of results of Cox regression models for the relation between TCDD ppt-years (CADM-based) and all cancer mortality. From Table III in Cheng et al. (2006).

Exposure Lag Period, TCDD Exposure Variable, and Model*	Coefficient Estimate for TCDD ($\hat{\beta}$)	Standard Error of $\hat{\beta}$
TCDD ppt-years, unlagged		
Full data, untransformed†	-8.9×10^{-9}	5.8×10^{-8}
Full data, ln-transformed	5.3×10^{-2}	3.1×10^{-2}
Excluding observations with ppt-years in the upper 1% range (2,409,588 and higher) of the exposures	3.6×10^{-7}	2.0×10^{-7}
Excluding observations with ppt-years in the upper 2.5% range (1,106,145 and higher) of the exposures	1.0×10^{-6}	3.2×10^{-7}§
Excluding observations with ppt-years in the upper 5% range (539,340 and higher) of the exposures	1.6×10^{-6}	6.2×10^{-7}§
TCDD ppt-years, lagged 15 years		
Full data, untransformed‡	1.7×10^{-8}	9.1×10^{-8}
Full data, ln-transformed	8.1×10^{-2}	2.9×10^{-2}§
Excluding observations with ppt-years in the upper 1% range (1,432,507 and higher) of the exposures	6.4×10^{-7}	3.2×10^{-7}
Excluding observations with ppt-years in the upper 2.5% range (661,664 and higher) of the exposures	6.4×10^{-7}	7.1×10^{-7}
Excluding observations with ppt-years in the upper 5% range (252,950 and higher) of the exposures	3.3×10^{-6}	1.4×10^{-6}§

*All models included year of birth and race; race: white or nonwhite; year of birth: quartiles of year of birth based on distribution of cancer decedents, with the first category as the referent.
†Range: 130–22,932,289 ppt-years.
‡Range: 6–17,284,554 ppt-years.
§$p < 0.05$.

Figure 1. Plot of Hill function relationship between y and x with EC50 parameter = 1 and exponent = 0.6.

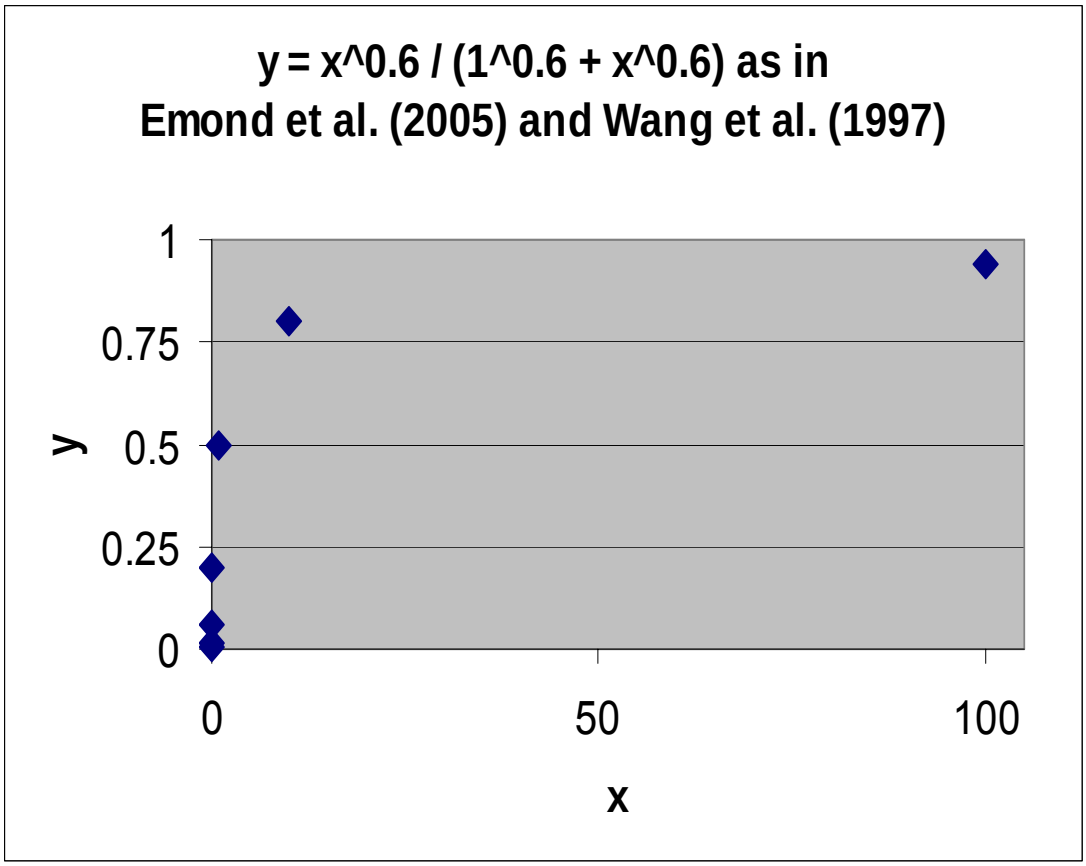

Figure 2. Ratio of measured to modeled serum lipid TCDD concentrations vs. CADM-modeled concentrations for the serum sampling subcohort (n=172) of the NIOSH cohort. Excerpted from Figure 4 in Aylward et al. (2005).

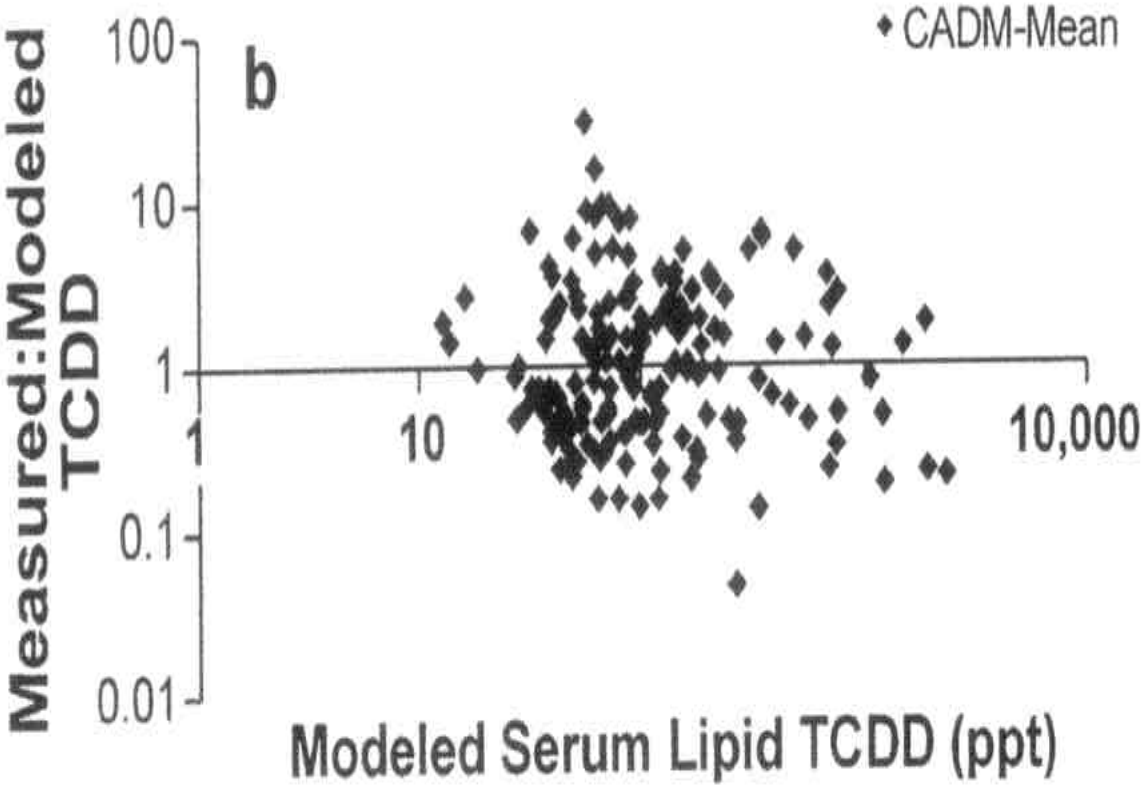

Figure 3. Measured serum lipid TCDD levels and best-fit CADM model results for two female Austrian patients of Geusau et al. (2002). Taken from Figure 4 of Aylward et al. (2005).

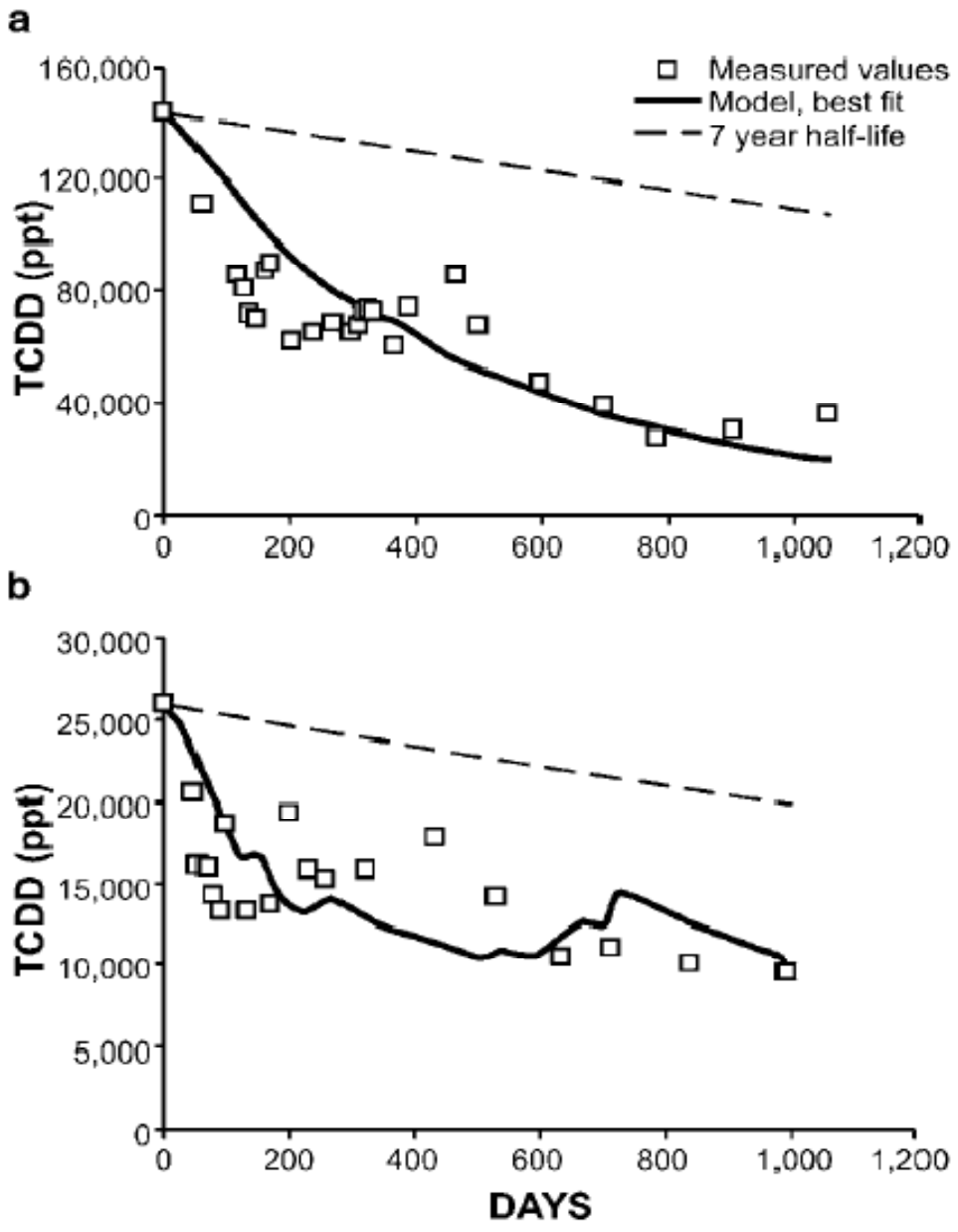
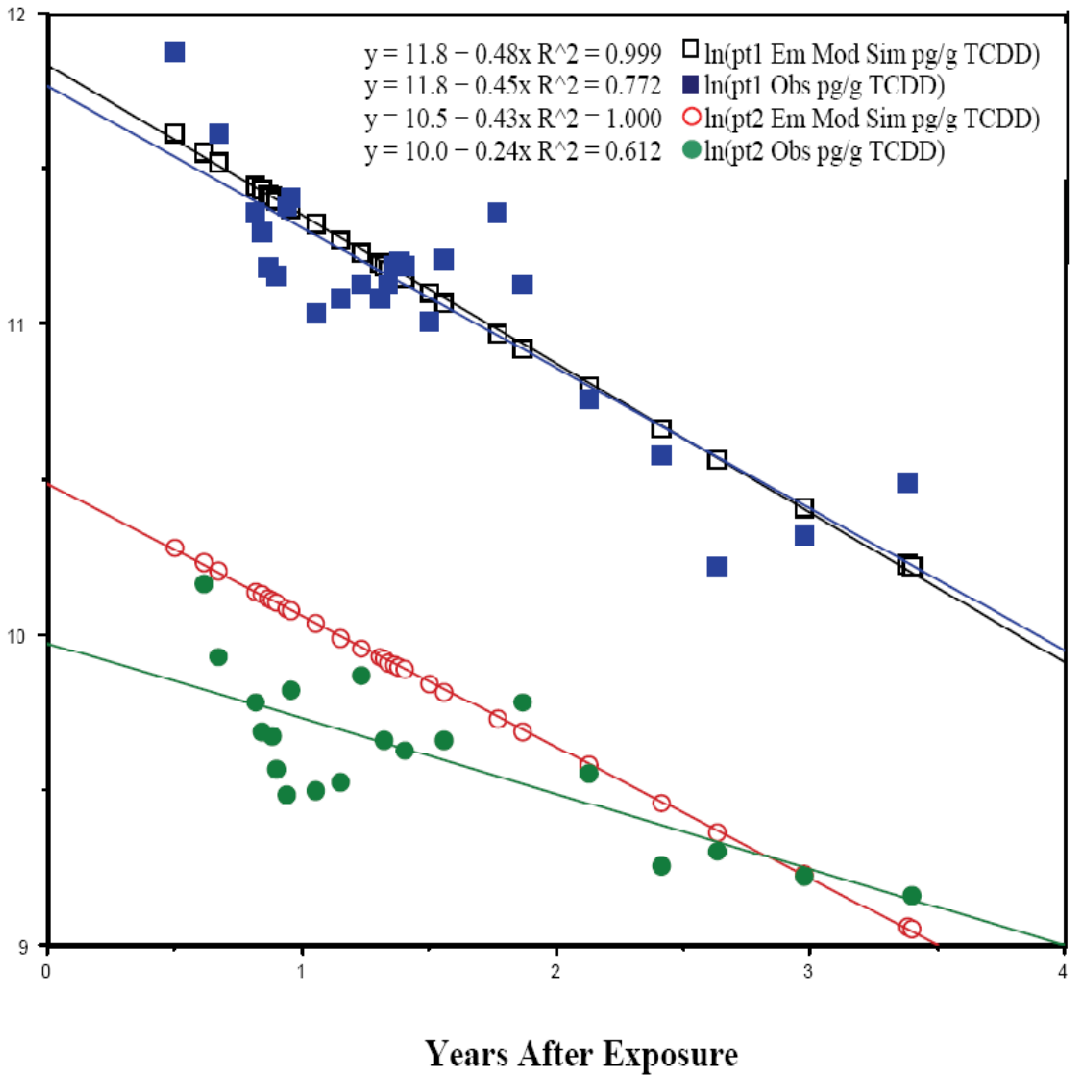
Figure 4. Observed vs. Emond et al. (2005) PBPK model-simulated serum TCDD concentrations in two Austrian women. Data from Geusau et al. (2002). Taken from Figure 3-18, p 3-87, of the new USEPA draft dioxin assessment document.