

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

**Prepared for the
American Chemistry Council
Washington DC**

**Prepared by
Thomas B. Starr, PhD & Principal
TBS Associates
Raleigh NC**

26 October 2010

1. Background

On 21 May 2010, USEPA released its response to key comments and recommendations made by the National Academy of Sciences (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.

My previous comments, submitted on 7 July (Starr 2010), focused on the latest approach taken by USEPA in assessing potential human cancer risks from exposure to dioxin-like compounds, specifically with respect to the risk-specific doses and "equivalent oral slope factors" (Tables ES-1, p liii, and 5-3, p 5-96) that the Agency uses to 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. The CADM model was calibrated and validated against measured serum TCDD concentrations for a subcohort of 172 workers from one of the eight NIOSH cohort plants. However, USEPA chose instead to utilize a different pharmacokinetic model, that of Emond et al. (2004, 2005, 2006), to produce its oral slope factors for human cancer risk.

I noted in my previous comments that this new approach to dioxin cancer risk assessment: 1) is 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: 1) serious and fundamental limitations of the Emond et al. PBPK model at low doses, and 2) the Agency's narrow interpretation of the epidemiology literature on dioxin exposure and human cancer, including the Cheng et al. (2006) reanalysis of the NIOSH cohort cancer mortality experience. My new comments presented herein further address these deficiencies, and specific recommendations to remedy them are provided. It is worth noting that the Emond et al. PBPK model was also utilized by USEPA in developing its Reference Dose (RfD) estimates for various noncancer endpoints. Thus, many of the shortcomings of the

Agency's approach to human cancer risk assessment are also directly relevant to the approach the Agency has taken to assessing human noncancer risks.

2. The serious deficiencies arising from the Agency's use of the Emond et al. PBPK model for low-dose extrapolation need to be corrected.

Tables ES-1 and 5-3 of the new risk assessment document show that USEPA's estimated human cancer risk has a *supralinear* dependence upon TCDD intake rate, with the estimated oral slope factor increasing by more than 10-fold, from 1.1×10^5 to 1.2×10^6 , as the associated risk level drops from 10^{-2} to 10^{-6} . In fact, the slope of the estimated cancer dose-response approaches *infinity* as the daily TCDD intake approaches zero. This is a completely nonsensical result, and I am aware of no physical, chemical, or biological system that responds with such infinite sensitivity to the smallest of perturbations.

In my previous comments, I noted that the *supralinearity* of USEPA's oral cancer slope factor originates in the dependence of cumulative TCDD exposure upon TCDD intake, which is in turn driven by the Emond et al. PBPK model's empirical Hill function relationship between CYP1A2 induction and the concentration of AhR-bound TCDD in liver. The Emond et al. model uses Wang et al.'s (1997) estimate of 0.6 for the Hill function shape parameter n , and it is well-known that any value of n less than 1 produces a *supralinear* dose-response relationship that is problematic at low doses.

There is, however, substantial and credible evidence that the Hill function shape parameter is no smaller than 1 for CYP1A2 induction. Walker et al. (1999) exposed female Sprague-Dawley rats to biweekly doses of 50, 150, 500, and 1750 ng TCDD in corn oil for 30 weeks and measured CYP1A1, CYP1A2, and CYP1B1 RNA levels in liver. Walker et al. fit Hill functions to these dose-response data and obtained a best-fit shape parameter estimate of 0.94 with a 90% confidence interval of (0.78, 1.14), for both CYP1A1 and CYP1A2 RNA. This value is not significantly different from 1. However, it is significantly greater than the 0.6 value employed in the Emond et al. (2005) PBPK model. Clearly, the 0.6 value used in the Emond model is questionable at best, and simply not credible on physical, chemical, and biological grounds.

In contrast, the CADM model of Aylward et al. (2005) employed standard Michaelis-Menten kinetics (a Hill function with shape parameter $n=1$) to describe CYP1A2 induction versus TCDD concentration in liver for humans. The CADM model therefore predicts a *linear* relationship between enzyme induction and liver TCDD concentration at low doses. Thus, the CADM model is well-behaved in the low-dose region and, as I noted in my previous comments, it does an excellent job of describing measured serum concentrations for the two acutely exposed patients studied by Geusau et al. (2002), as well as those for the subcohort of 172 workers from one of the NIOSH cohort plants.

RECOMMENDATION: The Emond et al. PBPK model should be replaced with the CADM model of Aylward et al. (1995) in all Agency calculations of potential human risk

in relation to TCDD serum levels or oral TCDD intake rates, for both cancer and noncancer endpoints.

3. The plant-specific mortality analyses from Cheng et al. (2006) must be given full and serious consideration. These implicate smoking as a major contributing factor in the observed excesses of all cancer, smoking-related cancer, and non-malignant respiratory disease mortality.

The Agency must consider fully other credible interpretations of the NIOSH cohort mortality data. For example, Cheng et al. (2006) presented standardized mortality ratio analyses of the NIOSH data for individual plants and for all eight plants combined. Table 1 summarizes these results for all cancer mortality, smoking-related cancer mortality, and mortality from non-malignant respiratory disease. Only one plant (plant 10) of the eight plants included in the all-plant analyses had significantly elevated all cancer mortality. If workers' TCDD exposures were truly responsible for the observed excess in overall all cancer mortality, one would expect the numbers of excess deaths to be distributed more or less proportionally to the expected numbers of deaths across the eight plants, but they are not! The excess deaths are concentrated primarily in plant 10. This suggests strongly that something other than TCDD exposure may have contributed to the excess all cancer mortality in this cohort.

Interestingly, mortality from smoking-related cancers, including lung cancer, was also significantly elevated at plant 10, as was mortality from non-malignant respiratory disease. In addition, smoking-related cancer mortality was significantly elevated at plant 8. This raises that distinct possibility that most of the excess in all cancer mortality that has been attributed to TCDD exposure across all the plants may in fact be due primarily to confounding by smoking (and/or other exposures to other workplace carcinogens) at just one plant! More than half (20) of the 36 excess all cancer deaths across all eight plants occurred among plant 10 workers, despite the fact that these workers accounted for only 10% (23) of the expected number of all cancer deaths (220) across the eight plants. Nearly two-thirds (13/20) of the excess deaths from all cancers at this plant were from smoking-related cancers. Furthermore, 23 (10+13) of the 24 (4+20) excess all cancer deaths in plants 8 and 10 were due to smoking-related cancers.

The Agency has not paid sufficient attention to the role that smoking and other, possibly plant-specific, chemical carcinogens, such as 4-aminobiphenyl and asbestos, may have played in elevating all cancer mortality in the NIOSH cohort workers. This is an especially critical consideration for TCDD, which is not a direct acting carcinogen, but rather, is thought to have a nongenotoxic, promotional mode of action (Starr 2003).

RECOMMENDATION: USEPA should make a concerted effort to account quantitatively for the impacts on its human cancer risk estimates of smoking and exposure to workplace carcinogens other than TCDD.

4. A threshold-based approach to cancer risk assessment for dioxins provides a credible alternative to linear low-dose extrapolation.

I noted in my previous comments 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 may be 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 argues strongly against a genotoxic mode of action. In fact, the weight of evidence strongly supports a nongenotoxic, promotional mode of action for TCDD, and a tissue concentration threshold may very well exist for this type of activity.

Consideration of the cancer mortality data from the three occupational cohorts (NIOSH, Hamburg, and BASF) in combination lends considerable support to the hypothesis of a threshold-like dose-response for all cancer mortality as a function of TCDD body burden, especially when allowance is made for elevated all cancer mortality in the absence of TCDD exposure. This is well-illustrated in Figure 1, adapted from Starr (2001). Interestingly, both Starr (2001) and Crump et al. (2003) found statistically significant positive intercept terms in their meta-analyses of data for these three cohorts, consistent with a significant elevation of all cancer mortality even in the absence of TCDD exposure. This remarkable feature of the combined data from the three occupational cohorts would not be readily apparent if the individual cohort data sets were analyzed separately. Figure 1 also shows clearly how very weak the overall all cancer mortality dose-response is, and strongly suggests a threshold body burden for TCDD effects on cancer mortality of ~50 ng/kg. USEPA cannot simply ignore these important findings from the Starr (2001) and Crump et al. (2003) meta-analyses.

RECOMMENDATION: USEPA should implement fully a threshold-based approach to human cancer risk assessment as a credible alternative to linear low-dose extrapolation.

5. Summary of Recommendations

- The Emond et al. PBPK model should be replaced with the CADM model of Aylward et al. (1995) in all Agency calculations of potential human risk in relation to TCDD serum levels or oral TCDD intake rates, for both cancer and noncancer endpoints.
- USEPA should make a concerted effort to account quantitatively for the impacts on its human cancer risk estimates of smoking and exposure to workplace carcinogens other than TCDD.
- USEPA should implement fully a threshold-based approach to human cancer risk assessment as a credible alternative to linear low-dose extrapolation.

6. References

Full citations are provided below only for those references not already cited in the 2010 USEPA draft document.

Aylward et al. (2005, 197014).

Cheng et al. (2006, 523122).

Crump KS, Canady R, Kogevinas M. 2003. Meta-analysis of dioxin cancer dose response for three occupational cohorts. *Environ Health Persp* 111(5):681-687.

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 (2001). Significant shortcomings of the US Environmental Protection Agency's latest draft risk characterization of dioxin-like compounds. *Toxicol Sci* 64:7-13.

Starr TB (2003, 594271).

Starr TB (2010). Comments on USEPA's Latest Draft Cancer Risk Assessment Approach for Dioxin-Like Compounds. Prepared for the American Forest and Paper Association, Washington DC. 13 pp. Dated 7 July 2010.

Walker et al. (1999, 198615).

Wang et al. (1977, 104657).

Table 1. Summary of results from plant-specific analyses of all cancer, smoking-related cancer, and nonmalignant respiratory disease mortality (NMRD) for the NIOSH occupational cohort. Adapted from Table II in Cheng et al. (2006).

Plant	Cause of Death								
	All Cancer			Smoking-Related Cancer*			NMRD		
	O/E	SMR	CI	O/E	SMR	CI	O/E	SMR	CI
1	42/38	111	80–150	17/17	99	58–159	10/11	94	45–172
3	21/18	116	72–178	12/7.6	157	81–275	5/5.4	93	30–217
4	13/15	90	48–153	6/6.2	97	36–211	1/4.5	22	1–124
7	2/3.3	62	8–223	2/1.5	133	16–481	0/0.8	0	0–479
8 [†]	22/18	125	78–189	18/8.1	224	133–353	9/4.7	191	87–363
9 [‡]	99/98	101	82–124	35/44	80	56–111	13/27	49	26–83
10 [¶]	43/23	187	135–252	24/11	225	144–335	12/6.0	200	103–349
13 [§]	14/7.8	180	98–301	6/3.8	157	58–342	2/1.9	106	13–384
Total [£]	256/220	117	103–132	120/99	122	101–145	52/61	86	64–112

Figure 1. Standardized mortality ratios (SMRs) and 95% confidence intervals for all cancer mortality versus estimated lifetime average TCDD body burden for the twelve study/exposure subgroups employed in the Starr's 2001 meta-analysis of all cancer mortality in three occupational cohorts. Adapted from Starr (2001).

