USEPA'S NEWEST RISK CHARACTERIZATION OF DIOXIN-LIKE COMPOUNDS IS SERIOUSLY FLAWED AND EXCESSIVELY CONSERVATIVE

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Introduction

The US Environmental Protection Agency's most current upper bound slope factor for estimating human cancer risk based on human data[1] was derived from a meta-analysis of data from three epidemiology studies of exposed workers: the Hamburg cohort[2], the NIOSH cohort[3], and the BASF cohort[4]. Both central (ED_{01}) and lower 95% confidence bound (LED_{01}) effective dose estimates of the lifetime average human TCDD body burden corresponding to a 1% increase in the lifetime risk of death from all-sites cancer, i.e., all-site cancer mortality, were generated. USEPA's ED_{01} and LED_{01} estimates were developed with Poisson regression using a linear dose-response model with an intercept constrained to equal unity: $SMR = 1 + \beta_1 D + \varepsilon$, where SMR is the Standardized Mortality Ratio for an exposure subgroup, D is the corresponding TCDD body burden in ng/kg and ε is an error term. Table 1 lists the all-site cancer mortality SMRs for the 12 exposure subgroups *versus* the corresponding lifetime average TCDD body burdens as determined by USEPA. The range of exposures spans more than three orders of magnitude, from 1.4 to 2012 ng/kg. Because the exposure range is so great, the combined data set provides an unusually rigorous test of a linear dose-response model, since the predicted incremental risk must also range linearly over the same 1,400-fold range. In this report, results from a formal meta-analysis of the epidemiologic data employed by USEPA and those from additional dose-response modeling are presented.

Initial meta-analysis

A fixed and random effects meta-analysis was conducted on the data in Table 1 using the Stata *meta* command (Stata Release 6, Stata Corporation, College Station TX). A meta-analysis of multiple epidemiologic studies is analogous to an analysis of variance (ANOVA) of multiple experimental studies, although the fact that epidemiologic studies are observational in nature can cause greater difficulty[5]. Weights assigned to each study estimate during the fixed and random effects analyses are also presented in Table 1. Results are summarized in Table 2. Especially noteworthy is the absence of any significant heterogeneity among the SMRs, as indicated by the large p-value of 0.355 for the heterogeneity test. This is surprising since 1) USEPA has asserted that there is a causal association between TCDD body burden and all cancer mortality; and 2) there is a marked difference in the TCDD body burdens that range over more than three orders of magnitude across the exposure subgroups. If a causal association between TCDD body burden and all cancer mortality were truly present, it would be expected to manifest as significant intergroup heterogeneity because no adjustment whatsoever for the large gradient in TCDD across the exposure subgroups has been made. This is a clear indication that any association between all cancer mortality and TCDD body burden in these data is so weak as to be undetectable in the meta-analysis. The extremely small estimate of

between studies variance (only 0.004) confirms the remarkable homogeneity of these exposure subgroups despite their marked TCDD exposure differences.

The pooled SMR estimates of 1.347 (fixed) and 1.343 (random) are virtually identical and significantly greater than one, indicating markedly higher all cancer mortality than is present in the comparison populations. However, as is shown in the next section, this elevation is not associated with TCDD exposure, so it is most likely attributable to the presence of significant cancer risk factors *other than TCDD exposure*. These cohorts had documented exposures to 4-amino-biphenyl, asbestos, and tobacco products in the workplace and possibly elsewhere, and adjustments for these and other potential risk factors such as lifestyle have not been entirely adequate in any of the studies.

Dose-response modeling

Table 3 presents results from conducting Poisson regressions of various dose-response models on the data set presented in Table 1. The first model considered was USEPA's linear model. The standard chi-square test revealed a highly significant lack of fit ($p = 0.0003$). Thus, USEPA's linear model provides an *inadequate* fit to the epidemiologic data. Given this marked discrepancy between epidemiologic fact and the default model predictions, it is difficult to justify use of this model to estimate points of departure or to conduct extrapolations to other exposure situations. A model cannot be trusted to perform well outside the data range in which it was estimated when it performs poorly within that range. The USEPA linear dose-response model is simply not credible.

Addition of a quadratic term to USEPA's linear model made no material difference in its performance as is indicated in the second row of Table 3; it still provides an inadequate fit to the data ($p = 0.0017$). It is only when USEPA's constraint of a unit intercept is relaxed that a linear model provides an adequate fit. With a floating intercept, a linear model provides a perfectly adequate description of the observations ($p = 0.313$), and addition of a quadratic term to this model does not materially affect its performance ($p = 0.237$). Even more interesting is the fact that an intercept only model is also perfectly adequate ($p = 0.310$). In the intercept only model there is no dependence whatsoever of risk on TCDD exposure. Instead, this model predicts that all of the exposure groups have the same, i.e., constant, elevation of all cancer mortality, by about 29%, relative to their respective comparison populations. This result is consistent with the presence of significant risk factors *other than TCDD exposure* in these work- places, as was noted earlier. Thus, the meta-analysis and the dose-response analyses both indicate that the worker's *TCDD exposure is not related to the apparent increases in their all cancer mortality.*

Sensitivity Analysis

The remaining rows of Table 3 present results for the floating intercept linear model with individual data points dropped out of the Poisson regressions. This exercise identified those data points, if any, that individually have an exceptionally large influence on the modeling results as expressed in the associated effective dose estimates. For example, elimination of the highest data point from the BASF study (2012 ng/kg) has a fairly strong impact on the estimated ED_{01}, increasing it 1.8-fold. This is not surprising, since this group's all cancer mortality SMR of 2.0 was higher than that for any other study group. Its elimination weakens the evidence in support of a positive linear relationship. Elimination of the highest data point from the NIOSH study (554.5 ng//kg) serves to reduce the estimated ED_{01} by 44%. This can be understood by noting that the SMR for this group (1.15) is lower

than one might expect, given their high TCDD body burden, if there were a causal association between TCDD exposure and all cancer mortality. Similarly, elimination of the lowest NIOSH study data point (27.8 ng/kg with an SMR of 1.02) serves to increase the estimated ED_{01} by 53%, presumably because its inclusion forces the predicted SMR at the low end of the exposure range closer to unity than do the other data points in the same range. Its elimination allows the model intercept to increase, while the model slope decreases to compensate. Inspection of the remainder of Table 3 reveals little more: elimination of any of the other data points one at a time makes little difference in the estimated ED_{01} or LED_{01}.

Impact of model selection on ED_{01} and LED_{01} estimates

Use of an adequate dose-response model has a dramatic impact on the estimated ED_{01}. The floating intercept model's ED_{01} is more than 3-fold higher than USEPA's fixed intercept linear model. Even the lower bound on the ED_{01}, known to be particularly robust to changes in model specifi- cation, is raised by 74% (49 ng/kg) relative to that for USEPA's inadequate model (28.1 ng/kg). Furthermore, if one were to hypothesize that the putative human carcinogenicity of TCDD were strictly a high dose, i.e., threshold, phenomenon, then dropping the highest BASF dose point from consideration could be justified on biological grounds. USEPA's ED_{01} estimate of 47.1 ng/kg would be increased by more than 5.5-fold to 261 ng/kg if an adequate floating intercept model of only the data below 2012 ng/kg were employed. It is worth noting finally that all of the adequate alternative models and truncated data sets considered herein yield ED_{01} and LED_{01} estimates that are considerably higher than those arising from USEPA's inadequate linear model. This justifies the conclusion that USEPA's ED_{01} and LED_{01} estimates are unrealistically low.

Conclusions

The epidemiologic data employed by USEPA to develop human cancer risk estimates are incompatible with the Agency's linear dose-response model, yet these data are entirely consistent with an intercept only model, a model with no slope component in relation to TCDD body burden. This conclusion provides strong quantitative support to previous assessments of the epidemiologic evidence regarding the potential human carcinogenicity of TCDD as *limited*, not sufficient. TCDD should continue to be classified by USEPA as, at most, a probable or likely human carcinogen. There is therefore no scientific basis for classifying it as a human carcinogen.

References

1. USEPA (2000). Exposure and human health reassessment of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds Part III: Integrated summary and risk characterization for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds. September 2000 SAB Review Draft. EPA/600/P-00/001Bg.
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4. Ott MG, Zober A (1996) *Occup Environ Med* 53:606-12.
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Table 1. Standardized Mortality Ratios (SMRs)), 95% confidence limits, and fixed and random effects weights assigned to each exposure subgroup.

Study Body Burden, ng/kg	Study SMR	95% CI on SMR Lower	Upper	Meta-Analysis Weights Fixed	Random
Hamburg 1.4	1.24	0.84	1.83	25.21	22.82
Hamburg 2.5	1.34	0.92	1.96	26.77	24.08
BASF 4.6	0.80	0.40	1.60	8.00	7.74
Hamburg 6.5	1.34	0.93	1.94	28.35	5.36
NIOSH 27.8	1.02	0.77	1.35	48.74	40.51
BASF 51.9	1.20	0.56	2.57	6.60	6.42
Hamburg 101.2	1.73	1.23	2.44	32.76	28.83
NIOSH 103.3	1.65	1.28	2.13	59.25	47.51
NIOSH 184.5	1.38	1.00	1.90	37.30	32.28
BASF 200.1	1.40	0.66	2.97	6.79	6.61
NIOSH 554.5	1.15	0.73	1.81	18.64	17.29
BASF 2012.0	2.00	0.89	4.47	5.93	5.79

Table 2. Summary of meta-analysis results.

Meta-analysis Method	Pooled SMR Estimate	95% CI on SMR Lower	Upper	Heterogeneity test: Q = 12.117 with 11 df (p=0.355)
Fixed	1.347	1.204	1.507	Between studies variance = 0.004
Random	1.343	1.191	1.515	(moment-based estimate)

Table 3. Goodness-of-fit statistics, ED_{01} and LED_{01} estimates for various dose-response models of all cancer mortality data from three epidemiologic studies in relation to TCDD body burden.

Dose-Response Model	Goodness-of-Fit χ^2	df	p-value	Point of Departure ED_{01}	LED_{01}^{95}
$1 + \beta_1 D$	28.1	11	.0003	47.1	28.1
$1 + \beta_1 D + \beta_2 D^2$	28.1	10	.0017	46.7	28.1
$\beta_0 + \beta_1 D$	11.6	10	.313	145.2	49.0
$\beta_0 + \beta_1 D + \beta_2 D^2$	11.6	9	.237	145.2	87.6
β_0	12.8	11	.310	NA	NA
$\beta_0 + \beta_1 D$ w/o 2012.	11.5	9	.234	261.0	36.0
w/o 554.5	10.0	9	.347	81.0	32.1
w/o 200.1	11.6	9	.237	146.3	49.1
w/o 184.5	11.6	9	.236	148.4	49.2
w/o 103.3	8.6	9	.471	141.5	49.5
w/o 101.2	8.9	9	.450	141.9	49.2
w/o 51.9	11.5	9	.242	146.9	49.2
w/o 27.8	11.6	9	.237	140.1	47.8
w/o 4.6	9.5	9	.392	168.9	51.9
w/o 2.5	11.6	9	.237	140.0	47.8
w/o 1.4	11.5	9	.242	150.3	49.3

NA: Point of Departure is not applicable to the intercept only model