

Comments on USEPA's Response to the NAS Report on the Agency's 2003 Dioxin Risk Assessment

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On behalf of the
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and American Wood Council

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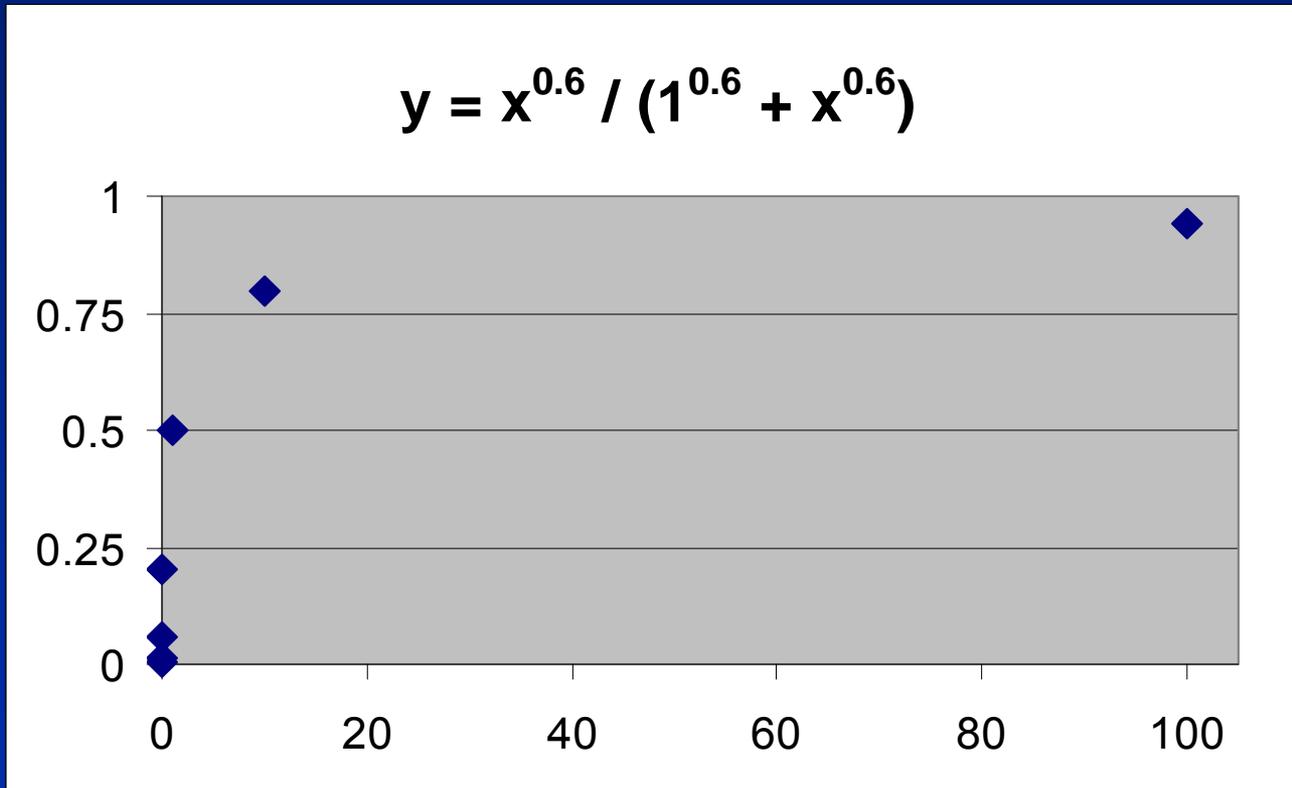
Three Critical Issues Need to be Addressed

- The Emond et al. (2004, 2005, 2006) PBPK model is seriously flawed
- USEPA's interpretation of Cheng et al. (2006) is far too narrow
- A comprehensive quantitative uncertainty analysis is necessary but altogether absent

From Tables ES-1 and 5-3

Lifetime Cancer Risk	AUC, ppt-yrs	Risk-Specific Dose, ng/kg/day	Slope Factor, (mg/kg/day) ⁻¹
10^{-2}	1.26×10^4	8.79×10^{-2}	1.1×10^5
10^{-6}	1.31×10^0	8.08×10^{-7}	1.2×10^6

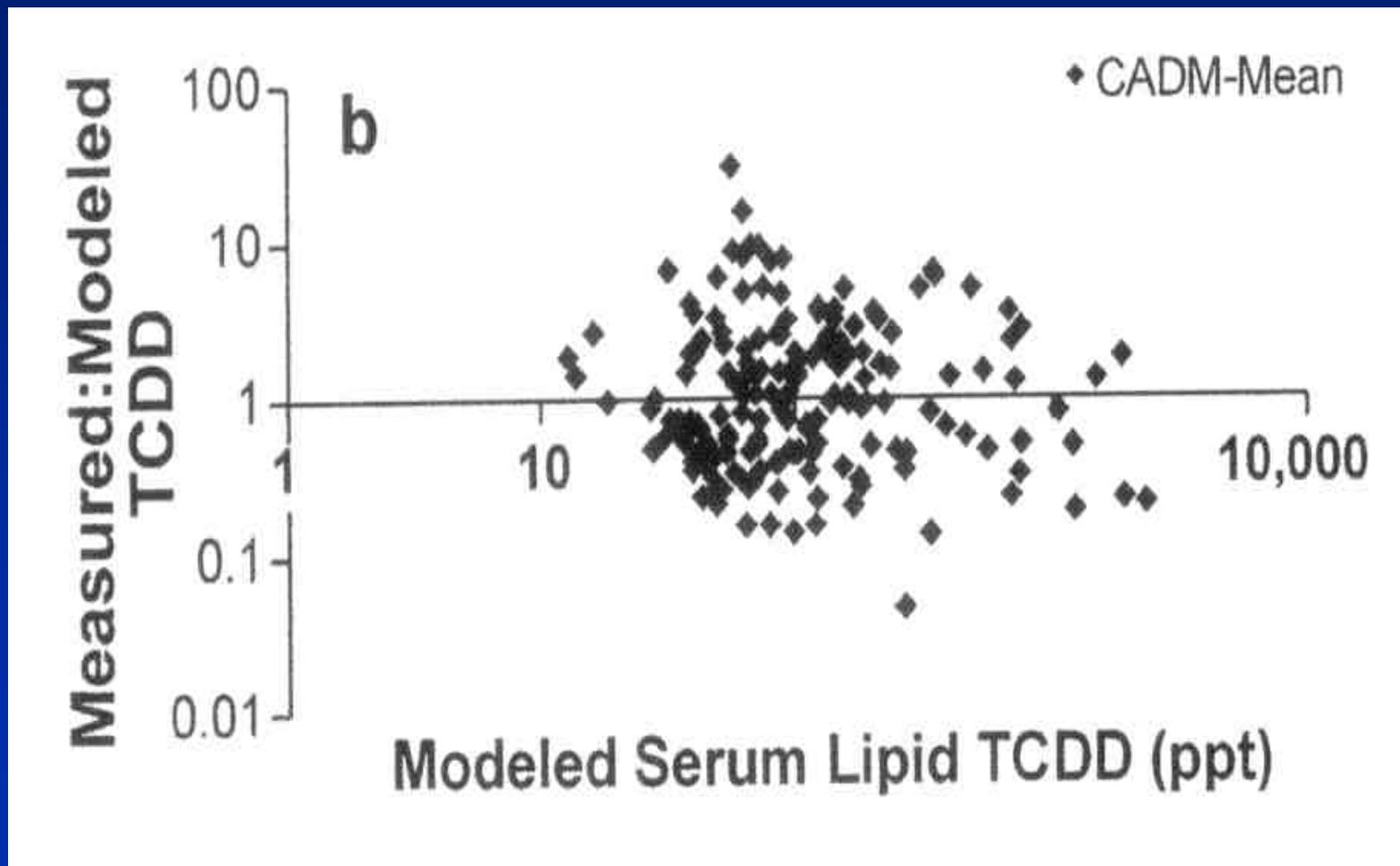
Emond et al. (2004, 2005, 2006) Hill Function: CYP1A2 induction vs AhR-bound TCDD



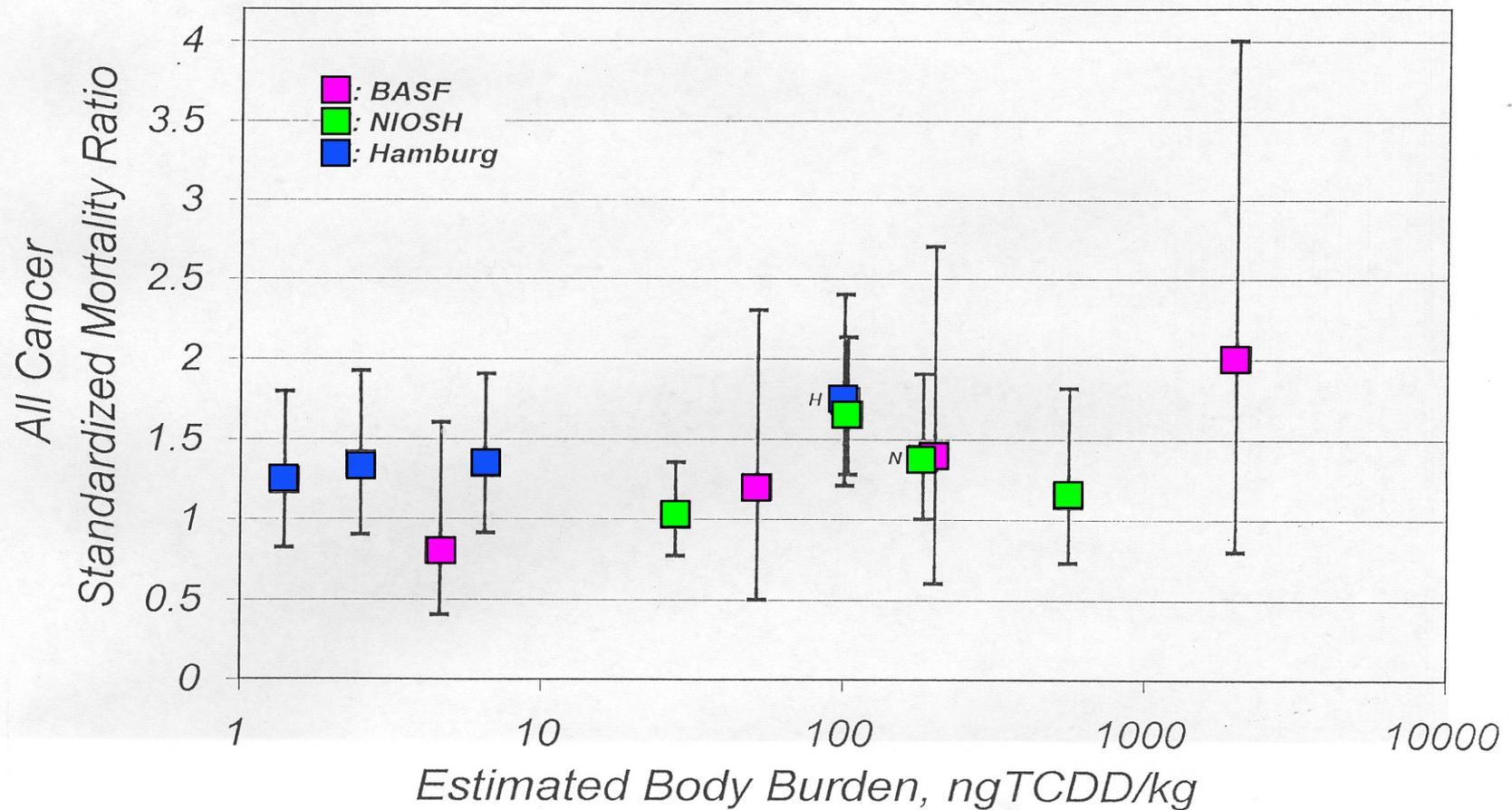
β Estimates: Table III Cheng et al. 2006

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}	$3.2 \times 10^{-7§}$
Excluding observations with ppt-years in the upper 5% range (539,340 and higher) of the exposures	1.6×10^{-6}	$6.2 \times 10^{-7§}$
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}	$2.9 \times 10^{-2§}$
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}	$1.4 \times 10^{-6§}$

Observed vs CADM-Predicted Serum Levels



Data from 3 Occupational Cohorts are Consistent with a Threshold ~ 100-1,000 ng/kg



Specific Recommendations

- Drop the problematic Emond et al. PBPK model
Use CADM for cancer and noncancer endpoints
- Undertake a comprehensive quantitative uncertainty analysis that includes pharmacokinetic, dose-response model-, and exposure-related uncertainties
- Recognize uncertainty explicitly in Tables ES-1 and 5-3:
Provide a range of credible risk-specific doses for each risk level
- Implement a threshold-based cancer model as a credible alternative to linear-through-zero extrapolation