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

Thomas B. Starr, PhD & Principal
TBS Associates, Raleigh NC USA

on behalf of the
American Chemistry Council

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Three Areas Need to be Addressed

- Choice of PBPK model for low-dose extrapolation
- Smoking and exposures to workplace carcinogens other than TCDD need to be addressed
- USEPA should implement fully a threshold-based approach to cancer risk assessment

Choosing a Reliable PBPK Model

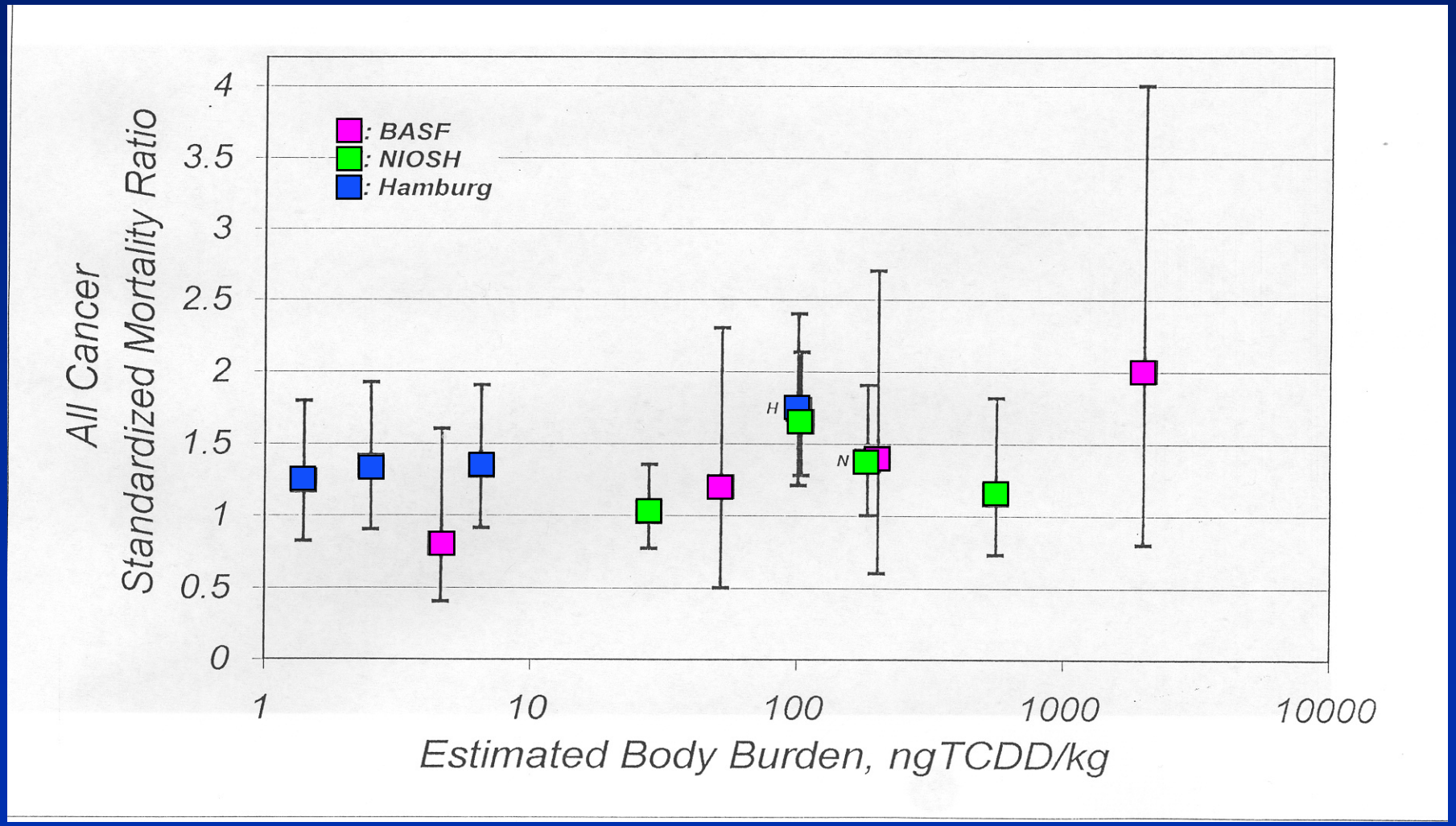
- Emond et al. PBPK model exhibits problematic *supralinear* behavior at low doses (n = 0.6)
- Walker et al. (1999) estimated n for CYP1A1 and CYP1A2 induction: n = 0.94 (0.78, 1.14)

- CADM uses n = 1 Hill kinetics
- CADM is calibrated and validated against worker serum levels *and* Gesau patient data
- Cheng et al. used CADM for exposure reconstruction

Plant-Specific SMR Analyses (Cheng et al. 2006)

	Cause of Death								
	All Cancer			Smoking-Related Cancer*			NMRD		
Plant	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

Data from the 3 Occupational Cohorts are Consistent with a Threshold ~ 50 ng/kg



Specific Recommendations

- Drop the problematic Emond et al. PBPK model

  Use CADM for cancer and noncancer endpoints

- Account for impacts on estimated risks of smoking and exposure to workplace carcinogens other than TCDD

- Implement fully a threshold-based approach as a credible alternative to linear low-dose extrapolation