Comments on TCDD Hepatocarcinogenicity Related to Threshold Dose-Response and EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds

Comments and views of:
James A. Popp DVM, PhD
Stratoxon LLC

Evaluation Supported by:
The Chlorine Chemistry Council

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Conclusion

- Extensive biological data indicates that TCDD hepatocarcinogenicity should be considered as a nonlinear dose effect for human risk assessment
  - Lack of genotoxicity
  - TCDD exposure related liver tumors are due to a tumor promotive effect of TCDD
  - Relationship exists between hepatocarcinogenicity and hepatotoxicity
  - Low-dose TCDD suppresses foci of cellular alteration and hepatocyte proliferation

Overview

- Extensive data available to interpret the rodent liver tumor response
- EPA document contains most if not all of the appropriate citations
- Interpretations and analysis of mode of action data for rat liver tumor response requires careful analysis beyond the EPA interpretation
- Presentation will identify and comment on 4 points regarding liver tumors

1. Genotoxicity

- No clear conclusion on genotoxicity in document
- EPA document:
  - Correctly concludes that “TCDD is not a direct genotoxic agent”
  - Questions whether TCDD may cause indirect DNA damage
  - Includes a conclusion that TCDD is a “complete carcinogen”
  - Does not adequately consider negative tumor initiation results

Genotoxicity
(continued)

- NAS Committee should assess all available data regarding genotoxicity considering the following points:
  - Evidence for lack of direct genotoxicity is overwhelming
  - Evidence that TCDD causes indirect genotoxicity is circumstantial
  - TCDD does not cause DNA adducts
  - Negative tumor initiation results in animals should be considered

2. Hepatic Tumor Promotion

- Numerous studies have documented the tumor promotive effect of TCDD
- Rat liver tumors result from promotion of spontaneously initiated sites
  - Demonstrated promotive effect
  - Negative genotoxicity including negative initiation studies
  - Concept is well established in the literature for tissues with spontaneous tumors

Hepatic Tumor Promotion
(continued)

- Consequences of carcinogenicity being due to promotion
  - Tumor promotion is generally recognized as having a threshold
  - TCDD promotion data on foci of cellular alteration not only suggests a threshold but suggests a reduction in these preneoplastic lesions related to low TCDD doses in animals

3. Hepatic Toxicity and Carcinogenicity

- EPA: “There is considerable controversy concerning the possibility that TCDD-induced liver tumors is a consequence of cytotoxicity”
  - Cytotoxicity noted in original and subsequent bioassays and experimental studies
  - Literature is confusing due to the imprecise use of the term “hepatotoxicity” which has been defined by:
    - Serum enzymes
    - Histopathology
    - Hepatocyte proliferation

Hepatic Toxicity and Carcinogenicity

(continued)

- Interrelationship of hepatic toxicity and carcinogenicity provides
  - Insight for understanding the mechanism of hepatocarcinogenicity
  - Important information for determining the relevance of the rodent tumors for assessing human risk
- These points inadequately explored in EPA's draft for dioxin-like compounds

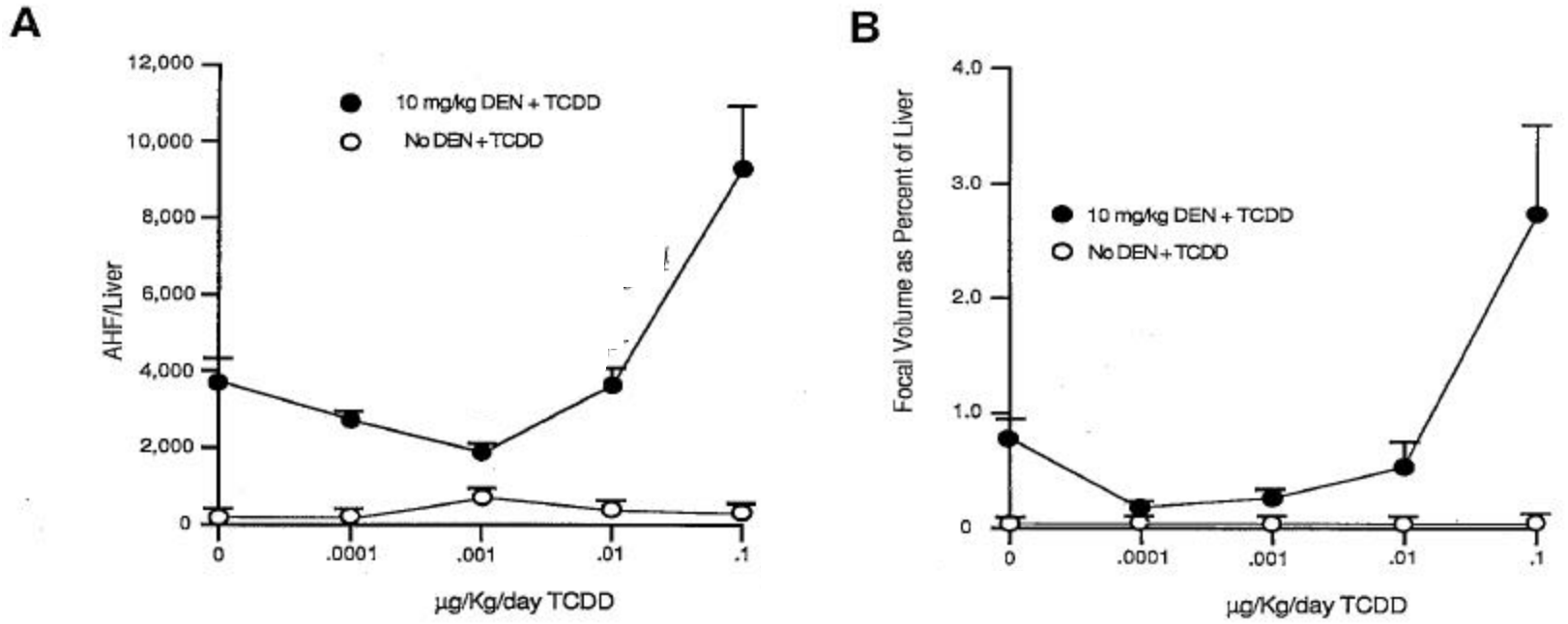
Hepatic Toxicity and Carcinogenicity
(Summarized Points)

- Clearly a dose-response relationship between hepatotoxicity and tumor formation (including enhancement of enzyme altered foci) supported by multiple studies
- Dose-response relationship of toxicity and carcinogenicity is different than the dose response relationship of enhanced gene expression and carcinogenicity
- Time-response difference between AhR enzyme induction and increased cell proliferation (indicator of hepatocyte lethality)
  - CYP 1A1 induction is very rapid
  - Cell proliferation noted many weeks after TCDD administration

Hepatic Toxicity and Carcinogenicity
Conclusion

- Liver tumors in rodents occur in the presence of hepatotoxicity with a dose-response relationship
- This interrelationship should be considered in detail since the interrelationship:
  - Is consistent with a biological threshold for carcinogenicity
  - Does not support a linear dose response for tumors

4. Low Doses of TCDD in Animals Suppress Foci Cellular Alteration



Pitot *et al.*, 1987 (Figure 4)

Low-Dose Effects of TCDD in Animals (continued)

- Number of foci of cellular alteration
- Focal volume of foci of cellular alteration
- Hepatocyte proliferation in non-focal hepatocytes is suppressed by low doses of TCDD
  - TCDD alone (Teeguarden et al 1999)
  - TCDD after DEN initiation (Maronpot et al 1993)

Low -Dose Effects of TCDD in Animals (Conclusion)

- Published data on the low dose effects of TCDD in animals does not support a linear dose response for TCDD carcinogenicity

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Discussion

Submitted to NAS Committee:

- “Weight of Evidence Analysis of the Cancer Dose-Response Characteristics of 2,3,7,8-Tetrachlorodibenzodioxin (TCDD)”

Hepatic Tumor Incidence in Sprague Dawley Rats

Goodman and Sauer 1992

	Group			
	C	**LD**	**MD**	**HD**
Dose (μg/kg)	0	0.001	0.01	0.1
No. tissues examined	86	50	50	45
Hepatocellular adenoma	2 (2%)	1 (2%)	9 (18%)	14 (31%)
Hepatocellular carcinoma	0	0	0	4 (9%)
Total animals with tumors	2 (2%)	1 (2%)	9 (18%)	18 (40%)

Hepatic Toxicity and Carcinogenicity
(First Data Set)

- Interrelationship of hepatic toxicity and carcinogenicity that should be fully considered:
  - Detailed reassessment of rat livers from the Kociba study resulted in the conclusion that "There appears to be a distinct correlation between the presence of overt hepatotoxicity and the development of hepatocellular neoplasms". Statement based on:
    - Comparison across dose groups for female rats
    - Male rats (no liver tumor response) have less toxicity than female rats

Hepatic Toxicity and Carcinogenicity
(Second Data Set)

- Maronpot et al noted a TCDD dose response hepatotoxicity as measured by histopathology and serum enzyme elevation
  - Dose related increase in hepatocyte DNA synthesis
  - High correlation was not found for labeling index and toxicity. However, a high correlation may not necessarily be expected because:
    - Histologic lesion represent events over long time period
    - Cell proliferation evaluation represents events over a short time period

Hepatic Toxicity and Carcinogenicity
(Third Data Set)

- Comparison of TCDD resistant and TCDD sensitive rat strains demonstrated a correlation between hepatotoxicity and foci of cellular alteration (surrogate for tumors)
  - No correlation between foci and induction of CYP 1A1
- Study stresses the importance of hepatotoxicity as a requisite step in tumor development in contrast to AhR related enzyme induction

Low Dose Effects of TCDD in Animals

- Effect of low doses of TCDD
  - Number of foci of cellular alteration
    - Pitot et al (1987) - suppresses foci
    - Teeguarden (1999) – threshold for foci
  - Focal volume of foci of cellular alteration