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CARCINOGENICITY SLOPE FACTOR FOR 2,3,7,8-TCDD: OVERVIEW AND RECENT DEVELOPMENTS

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The slope factor for 2,3,7,8-TCDD calculated by MDNR, EPA, and other agencies has been based upon the female rat bioassay of Kociba et al. (1978). In 1980 the histopathologic slides from that bioassay were evaluated by Dr. Robert Squire, an independent pathologist and consultant to the EPA Carcinogen Assessment Group (CAG). The analyses of the data by Drs. Kociba and Squire formed the basis for CAG's calculation of the slope factor of 1.56×10^{5} $(mg/kg/d)^{-1}$ for total significant tumors in female rats, which included liver tumors, lung tumors and tumors of the nasal turbinates/hard palate (EPA, 1984; 1985). This slope factor is the geometric mean of the slope factors obtained from the Kociba analysis (1.51×10^{5}) and the Squire analysis (1.61×10^{5}) after adjustment for early mortality by eliminating those animals that died during the first year of study (EPA, 1985). The slope factor derived by MDNR/SWQD is 1.51×10^{5} $(mg/kg/d)^{-1}$, from the Kociba analysis for female rat liver tumors only. Slope factors used by FDA, CDC and California are reportedly based on either the Kociba or Squire analysis of liver tumors only (EPA, 1988).

In 1989, industry groups argued to the Maine Science Advisory Panel (SAP) that a reevaluation of the histopathologic slides of Kociba et al. (1978) was necessary (BNA, 1990). The reevaluation, they argued, would yield a lower potency estimation if the National Toxicology Program's 1986 liver tumor classification scheme were followed. In January 1990, Dr. Squire supported that contention in a letter to the Maine SAP in which he reported that his blind, preliminary re-reading of the slides indicated substantially lower tumor incidences. The Maine SAP requested that an objective review of the evidence be conducted. PATHCO, a pathology contractor, subsequently organized a panel of seven independent pathologists referred to as the Pathology Working Group (PWG).

In March 1990 under observation by Dr. Moch of FDA and Dr.'s Singh and Chiu of EPA, the PWG blindly reevaluated the female liver slides according to the NTP's 1986 liver tumor classification scheme (Sauer, 1990). The tumor incidence rates recorded by the PWG were lower than those of Kociba et al. (1978) or Squire in 1980, with carcinomas present only in the high dose group (see Table 1). The PWG reanalysis results in a slope factor based on liver tumors only that is approximately one-third of the current MDNR slope factor (5.2×10^{4} vs. 1.51×10^{5}). The slope factor for total significant tumor risk, utilizing the PWG analysis for liver tumors, is approximately one-half the current MDNR slope factor (7.5×10^{4} vs. 1.51×10^{5}).

Table 1. Tumors Significantly Increased in Kociba et al. (1978) with Liver Tumor Analysis by a) Kociba et al. (1978) and b) PWG (1990).

Primary Neoplasm	Dose Level (ug/kg/d) 0	0.001	0.01	0.1
lung: pulmonary adenocarcinoma/ squamous cell carcinoma	0	0	1	7
nasal turbinates/hard palate: squamous cell carcinoma	0	0	1	4
liver:				
a. Kociba (as reported in EPA (1984))				
hepatocellular hyperplastic (neoplastic) nodule	8	3	18	23
hepatocellular carcinoma	1	0	2	11
*total liver-tumor-bearing animals	9	3	18	34
b. PWG (1990)				
adenoma	2	1	9	14
hepatocellular carcinoma	0	0	0	4
**total liver-tumor-bearing animals	2	1	9	18
***Total tumor-bearing animals (with Kociba liver analysis)	9	3	18	34
****Total tumor-bearing animals (with PWG liver analysis) (Bayard, 1990)	2	1	10	24
Total number animals at risk ($\geq$ 12 mo. survival)	85	48	48	40

* $q_1^* = 1.51 \times 10^5$ $(mg/kg/d)^{-1}$ ← currently used by DNR

** $q_1^* = 5.2 \times 10^4$ $(mg/kg/d)^{-1}$ ← using re-evaluated liver tumors

*** $q_1^* = 1.51 \times 10^5$ $(mg/kg/d)^{-1}$

**** $q_1^* = 7.5 \times 10^4$ $(mg/kg/d)^{-1}$ ← using total tumors

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