

ATTACHMENT M

Selection of a Cancer Slope Factor for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

In its Human Health Risk Assessment (HHRA), EPA has evaluated potential cancer risks from exposures to dioxins, furans, and “dioxin-like” PCB congeners, all converted to toxic equivalents (TEQs) of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), using a cancer slope factor (CSF) of 150,000 (mg/kg-day)⁻¹ for TCDD. In addition, in its uncertainty analyses, the HHRA notes that EPA’s 2000 draft Dioxin Reassessment recommends use of a CSF of 1,000,000 (mg/kg-day)⁻¹ for TCDD, which would result in increased risks from TEQs, and that thus the cancer risks calculated for TEQs in the main HHRA may be underestimated (Vol. I, pp. 2-33, 5-33; Vol. IIIA, p. 7-8; Vol. IV, p. 7-14).

The carcinogenic dose response for TCDD is highly controversial and is an ongoing matter of scientific debate. EPA has never adopted a CSF for TCDD. The CSF used in the HHRA of 150,000 (mg/kg-day)⁻¹ is based on an early evaluation by EPA (1985) of the histopathology of the Kociba et al. (1978) rat study, has been used historically, and was previously listed in EPA’s Health Effects Assessment Summary Tables (HEAST). However, neither that value nor any other CSF for TCDD is currently listed on HEAST and none has ever been listed in EPA’s IRIS database. Moreover, since that CSF was derived, both the tumor classification scheme recommended by the National Toxicology Program (NTP) and the cross-species scaling factor used to scale results from rats to humans have been revised, as discussed further below.

Since the early 1990s, a wide range of CSFs, spanning from 9,000 to 1,000,000 (mg/kg-day)⁻¹, have been derived using a linear, non-threshold cancer model (Keenan et al., 1991; FDA, 1993, 1994; EPA, 2000). The differences in the CSFs are the result of the selection of the tumor classification scheme used to calculate tumor incidence rates and the inter-species scaling factor used to scale results from rats to humans. Currently, the toxicity of TCDD is under review as part of EPA’s draft Dioxin Reassessment. During the review of that Reassessment, the assignment of a CSF to TCDD has been controversial and external peer reviewers have been unable to achieve a consensus. In fact, in reviewing the draft Reassessment, EPA’s Science Advisory Board (EPA, 2001) stated that there was no consensus opinion on whether TCDD should be classified as a human carcinogen or on whether the modes of action for animals and humans are similar (p. 44). In addition, disagreement among Panel members concerning the

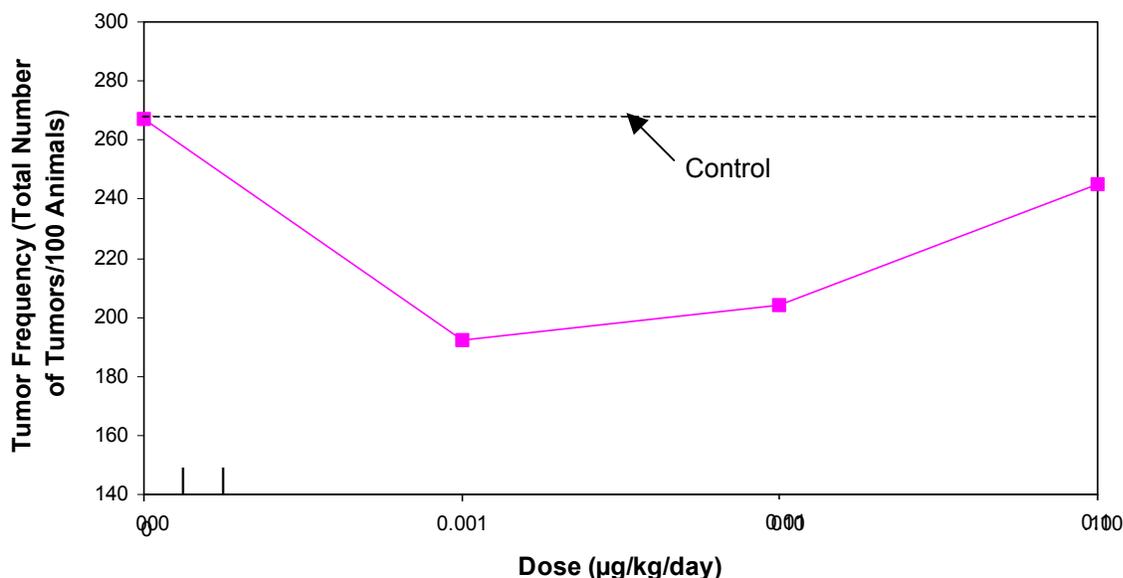
appropriate extrapolation model to be used resulted in the conclusion that the Panel could not “reach consensus on a single value for a dioxin potency factor” (p. 6).

Further, due to substantial questions about the scientific underpinnings of the draft Reassessment’s conclusions about the toxicity of dioxin and dioxin-like compounds, Congress has directed EPA to undertake an agreement with the National Academy of Sciences (NAS) to review that document (House of Representatives, 2003). The key issues to be reviewed by the NAS are to include “the validity of the non-threshold linear dose-response model in light of epidemiological studies and the corresponding cancer slope factor calculated by the Agency through use of this model” (House of Representatives, 2003, pp. 1445-46).

As indicated by the above quotation, there is considerable controversy in the scientific community as to the validity of a linear non-threshold model for TCDD. Since publication of the SAB Report (EPA, 2001), review of epidemiological, laboratory animal, and mechanistic data has led many scientists to support a threshold model for dioxin cancer and non-cancer effects (EPA, 2001; Pohl et al., 2002; Starr, 2001). Further, other scientific or regulatory bodies have offered their views on this issue. For example, a report of the Joint Expert Committee on Food Additives (JECFA) of the World Health Organization noted that “a tolerable intake could be established for TCDD on the basis of the assumption that there is a threshold for all effects, including cancer” (JECFA, 2001). Similarly, the European Commission Health & Consumer Protection Directorate-General Scientific Committee on Food models the data using a threshold model for cancer risk (EC-SCF, 2001). In a recent paper, the Agency for Toxic Substances and Disease Registry (ATSDR) stated that it continues to support its minimal risk level (MRL), established in 1998 (ATSDR, 1998), of 1 pg/kg-day (Pohl et al., 2002). ATSDR believes that this daily level is adequately protective of both cancer and non-cancer effects.

As a further illustration, the original rat data of Kociba et al. (1978) on the dose response of female Sprague-Dawley rats to TCDD can be rearranged in the form of the tumors for specific organs for a range of doses. EPA (1985) based its estimate of cancer risk only on elevated tumors in female rat livers at the two highest doses. However, the tumor rate even for female rat livers at the lowest dose was significantly lower than that experienced by the controls. Moreover, for total tumors of all types in all tissues in the females, the data reveal a strongly negative (i.e., anti-carcinogenic), U-shaped relationship between dose level and tumors at the lower doses, as depicted in the figure, below.

Tumor Frequency of Female Rats Exposed to TCDD



Nevertheless, even accepting the framework of EPA's procedures and linear non-threshold model, GE does not believe that the HHRA should use the CSF of 150,000 (mg/kg-day)⁻¹ because it was based on a now-outdated tumor classification scheme and a now-outdated method for scaling results from rats to humans. As noted above, there is no current EPA guidance or policy that would constrain EPA to use that CSF. As discussed elsewhere in these comments, GE believes that the TEQ approach and the application of any CSF for TCDD should not be used for evaluating potential cancer risks associated with PCB congeners. However, to the extent that EPA uses a CSF for TCDD to assess potential cancer risks of PCDDs and PCDFs, and assuming that it continues to adhere to a linear non-threshold model, GE recommends use of a CSF of 30,000 (mg/kg-day)⁻¹ for TCDD. This factor is based on the revised tumor incidence rates reported by an independent Pathology Working Group (PWG, 1990a,b) for liver tumors in the Kociba et al. (1978) study, along with use of the inter-agency compromise inter-species scaling factor, as described below.

In 1990, the rat liver slides from the Kociba et al. (1978) study were re-evaluated by a group of independent pathologists using new criteria for classifying proliferative rat liver lesions (PWG, 1990a,b). These criteria were developed and published by the NTP (Maronpot, et al., 1986; McConnell et al., 1986; NTP, 1986) and adopted by EPA (1986) as policy. Specifically, these

criteria differentiated between two types of lesions that had previously been grouped together as neoplastic nodules: hepatocellular adenomas, a benign neoplasm, and hyperplasia, a non-neoplastic response. Based on the PWG (1990a,b) re-evaluation of the liver slides from the Kociba et al. (1978) study, it was determined that the original tumor incidence rate had been overstated by inclusion of non-neoplastic lesions (i.e., hyperplasia).

Following this re-evaluation, revised CSFs were calculated for TCDD by Keenan et al. (1991) and the U.S. Food and Drug Administration (FDA) (1993), following the same general approach as EPA (1985) (i.e., using a linear, non-threshold model), but using the results of the PWG (1990a,b) reanalysis. In doing so, Keenan et al. (1991) and FDA (1993) based their CSF estimates on the combined incidences of liver tumors (hepatocellular carcinomas and adenomas) from the re-evaluation of the Kociba et al. (1978) study, rather than on the combined incidence of liver, lung, and nasal turbinate tumors from that study, as had been originally done by EPA (1985). Because Kociba et al. (1978) attributed the development of lung and nasal turbinate tumors to an artifact of the study -- the incidental inhalation of food particles not likely related to the ingestion pathway -- it was believed that these should not be counted in the CSF derivation. In addition, Keenan et al. (1991) and FDA (1993) used the FDA approach for extrapolating the results of rodent carcinogen bioassays to humans, performing cross-species scaling of daily doses on the basis of body weight raised to the first power [(body weight)¹]. Using this approach, Keenan et al. (1991) derived a CSF of 9,700 (mg/kg-day)⁻¹ for TCDD, and FDA (1993) derived a similar CSF of 9,000 (mg/kg-day)⁻¹ for use in its risk assessments.¹

In recognition of the differences between the scaling factors used by EPA and FDA, and in an effort to develop a unified approach for use in cases where agent-specific data were limited, FDA, EPA, and the Consumer Product Safety Commission (CPSC) proposed a unified compromise inter-species scaling approach, which assumes that intakes differ among mammalian species when daily doses are in proportion to body weight raised to the 3/4 power [(body weight)^{3/4}] (EPA 1992). That approach was used by EPA (1996) in its reanalysis of the carcinogenic potency of PCBs.

¹ More recently, using EPA benchmark dose software in accordance with EPA's *Interim Final Guidelines for Carcinogen Risk Assessment* (EPA, 1999) for a low-dose linear model, AMEC calculated a similar CSF for TCDD of 9,600 (mg/kg-day)⁻¹. As with the FDA (1993) and Keenan et al. (1991) values, this CSF represents cross-species scaling of daily doses on the basis of body weight raised to the first power.

When this compromise scaling approach is used in conjunction with the PWG (1990a,b) reevaluation of the liver tumor incidence rates from the Kociba et al. (1978) study and the FDA (1994) extrapolation method, it results in a CSF of 30,000 (mg/kg-day)⁻¹. FDA used that resulting CSF of 30,000 (mg/kg-day)⁻¹ to calculate a second estimate of upper-bound risk from TCDD (FDA, 1994). GE recommends that, assuming adherence to a linear non-threshold model, this CSF should be used for assessing the carcinogenic risks of dioxins and furans (as TEQs) in the HHRA.

In addition, and in any event, GE believes that EPA should not use the proposed new CSF of 1,000,000 (mg/kg-day)⁻¹ for TCDD, which is contained in the draft Dioxin Reassessment (EPA, 2000), even in its uncertainty analyses. That document has undergone some changes since the 2000 draft cited in the HHRA, and EPA makes clear on its own website (<http://cfpub.epa.gov/ncea/cfm/dioxin.cfm>) that the draft Dioxin Reassessment “should not be construed to represent Agency policy or factual conclusions” and “should not be cited or referred to as EPA’s final assessment of dioxin risks.” Moreover, as also discussed above, that document is required by a Congressional directive to be submitted to the NAS for review, based on concerns over its validity, and the issues to be reviewed specifically include the validity of the recommended CSF for TCDD. Prior to the completion of this review, it is inappropriate and unwarranted to use the draft’s proposed CSF in a site-specific risk assessment, even as part of an uncertainty analysis, to suggest that the cancer risks calculated for TEQs may be underestimated.

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