Scientific debate about the potential human carcinogenicity of dioxin-like compounds has been ongoing for nearly 25 years, and recent meta-analyses of data from three occupationally exposed cohorts have reached such different conclusions that the debate is certain to continue. The first meta-analysis [U.S. Environmental Protection Agency (U.S. EPA) 2000] produced an upper-bound estimate of the additional risk of death from any cancer of approximately $10^{-3}$ per picogram per kilogram per day for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) intake, which the U.S. EPA generalized to all “dioxin-like” compounds via toxic equivalency factors (TEQs). This potency estimate implies that about 4,000 additional cancer deaths occur per year in the United States solely from background intake of dioxin-like compounds [about 1 pg toxic equivalents (TEQ)/kg/day], 95% of which comes from normal dietary sources, and only 10% of which is due to TCDD (U.S. EPA 2000).

Subsequently, in 2001, I (Starr 2001) showed that the U.S. EPA’s model did not fit the data adequately because it failed to account for a significant baseline elevation of all cancer mortality in the three cohorts; this meta-analysis demonstrated that “these data are entirely consistent with an intercept-only model, a model that has no slope component whatsoever in relation to estimated TCDD body burden,” which implies zero additional human cancer deaths from any and all exposures to dioxin-like compounds. Finally, Crump et al. (2003), using updated data for the National Institute for Occupational Safety and Health (NIOSH) cohort (Steenland et al. 1999, 2001), concluded that their meta-analysis “provides some evidence that TEQ exposures near current background levels are carcinogenic.”

How is it possible for different investigators to reach such markedly different conclusions from similar analyses of essentially the same data? The answer lies in a) a failure to allow for causes of elevated cancer mortality other than dioxin exposure; b) differences in choices for a dose metric; c) selective use of different assumptions regarding the elimination half-life of TCDD in humans; and d) selective use of different assumptions regarding the impact on cancer mortality of the most recent 15 years of exposure. Resolution of the disparate conclusions will require detailed worker exposure data for TCDD and for direct-acting carcinogens, as well as a more general dose-response model that adequately reflects TCDD’s characteristics as a promoter.

**Selection of a Dose Metric**

*Average TCDD body burden.* The U.S. EPA (2000) and I (Starr 2001) both employed average TCDD body burden as the dose metric. Fingerhut et al. (1991), in a study of the NIOSH cohort (5,172 workers from 12 U.S. plants), provided all cancer standardized mortality ratios (SMRs) for four exposure duration categories—< 1, 1 to < 5, 5 to < 15, and ≥ 15 years—all with at least 20 years elapsed since first exposure; SMRs [95% confidence intervals (CIs)] for these categories are 102 (95% CI, 77–135), 165 (95% CI, 128–213), 138 (95% CI, 100–190), and 115 (95% CI, 73–181), respectively. Fingerhut et al. (1991) observed a total of 162 cancer deaths through the end of follow-up (31 December 1987) among the 3,036 men included in this analysis. The inverted dose response with increasing exposure duration is worth noting.

Aylward et al. (1996) subsequently used serum sample data for 253 workers from 2 of the 12 NIOSH cohort plants to compute average serum lipid TCDD concentrations (temporally averaged from birth through death or the end of follow-up). The sampled workers received their last occupational exposures to TCDD from 15 to 37 years before the sampling date (Piacitelli et al. 2000), necessitating a back-extrapolation from the measured concentration on the sampling date to earlier values assuming a 7.5-year elimination half-life for TCDD. Aylward et al. (1996) also assumed constant exposures during the occupational exposure period and a 5-ppt baseline serum lipid level before the date of first occupational exposure. Group means were estimated by averaging the values for sampled workers in each of Fingerhut et al.’s (1991) four duration categories.

Assuming a body fat content of 25% by weight, the U.S. EPA (2000) calculated equivalent average TCDD body burdens via division by a 4-fold factor. Details of similar average body burden calculations for the four Hamburg cohort exposure categories (totaling 124 cancer deaths among 1,189 men; Flesch-Jansy et al. 1998) and the four BASF cohort (BASF AG, Ludwigshafen, Germany) exposure categories (totaling 31 cancer deaths among 243 men; Ott and Zober 1996) have been published previously (Starr 2001; U.S. EPA 2000) and so are not repeated here.

*Cumulative TCDD exposure score.* Steenland et al. (1999) extended follow-up for a subset of the original NIOSH cohort (8 of 12 plants) by 6 years and used an exposure assessment (Piacitelli et al. 2000) that quantified worker’s exposures during employment with a score equal to the sum of products of a) the concentration of TCDD in process materials; b) the fraction of the day each worker spent on each process; and c) a “qualitative contact level” (0.01–1.5) based on the...
potential for inhalation of contaminated dust and the amount of contamination thought to reach exposed skin areas. A cumulative exposure score was generated for the 3,538 workers in their “exposure-level” cohort, which included 256 cancer deaths, about 58% more deaths than were included in Fingerhut et al.’s (1991) earlier analysis by exposure duration.

Although Steenland et al. (1999) conducted unlagged analyses with their cumulative exposure score, they focused attention primarily on results obtained when their cumulative exposure scores were lagged by 15 years, in keeping with a common epidemiologic practice of assuming that cancer cannot result from exposure until after a prolonged latency period. For example, if workers’ cumulative exposure had occurred solely during the most recent 15 years of follow-up, these workers were considered by Steenland et al. to be unexposed in their lagged analyses, and their person-years of experience were allocated to the lowest of their seven exposure categories, irrespective of how great the workers’ actual cumulative exposure scores may have been.

Among workers who were assigned to Steenland et al. ’s (1999) lowest exposure category solely by virtue of the 15-year lag assumption, there were 40.2 cancer deaths expected, but only 33 were observed, yielding an SMR of 82 (95% CI, 58–115) among these men defined by assumption to have little or no exposure against the back-extrapolated serum lipid TCDD values by linear regression. For the 170 workers with measured TCDD levels greater than the measured serum levels, whereas Steenland et al.’s (2001) back-extrapolated values were between only 2\(15/8.7\) = 3.3 and 2\(15/7.8\) = 19.1 times larger, that is, about 18–38% smaller than Aylward et al.’s values. This produces a corresponding inflation of their cumulative exposure scores and the back-extrapolated serum lipid TCDD concentration, as predicted by Steenland et al.’s (2001) linear regression, but lagged 15 years. It is important to note here that Steenland et al. (1999) purposefully excluded from their analysis 727 TCDD-exposed workers that had been included in Fingerhut et al.’s (1991) original analysis; Steenland et al.’s stated reason was that 727 workers with exposure to both pentachlorophenol and TCDD were eliminated to avoid possible confounding of any TCDD effects by pentachlorophenol. Pentachlorophenol is contaminated with higher chlorinated dioxins. These dioxins and TCDD are thought to act similarly with regard to the Ah receptor and gene expression, although they are considered less toxic.

Ironically, this “similarity of action” is the reason Crump et al. (2003) added 2,700 ppt-years of non-TCDD background TEQ to their dose metric for the NIOSH cohort (and 3,000 ppt of TEQ to the Hamburg and BASF cohort values as well) before conducting their trend analyses (i.e., because they presumed that non-TCDD congeners should be included after taking account of relative potency differences via TEFs). The assumption that polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and the dioxin-like coplanar polychlorinated biphenyls can be combined, using TEFs, into a single exposure metric (TEQ) suitable for use in human cancer risk assessment has been embraced by the U.S. EPA (2000) and the World Health Organization (Van den Berg et al. 1998), among others, but this simplistic approach to complex mixtures of dioxin-like compounds is not without controversy (e.g., Starr et al. 1997, 1999).

For the Hamburg cohort, Crump et al. (2003) selected SMR data for quartiles of unlagged cumulative serum lipid TEQ concentration above background as provided in Table 6 of Flesch-Janys et al. (1998). Because Crump et al.’s dose metric for this cohort was estimated with a 7.2-year half-life for TCDD (Flesch-Janys et al. 1996) and no lag, whereas their NIOSH dose metric was estimated with an 8.7-year half-life and a lag of 15 years, there is a substantial downward shift of the NIOSH cohort’s data points on the cumulative exposure scale relative to those for the Hamburg cohort.

To illustrate, suppose that a Hamburg cohort worker had a measured serum TCDD concentration of 1,000 ppt but had not been occupationally exposed during the 15 years immediately preceding the measurement. Then the contribution from those 15 years to
his cumulative TCDD exposure on the date of measurement would be 33,633 ppt-years using Flesch-Janys et al.'s 7.2-year TCDD half-life (Flesch-Janys et al. 1996) and no lag. For a worker from the NIOSH cohort with the same measured concentration, Steenland et al.'s 8.7-year half-life (Steenland et al. 2001) gives a corresponding contribution to cumulative TCDD exposure of only 28,916 ppt-years, about 4,717 ppt-years smaller. However, with the 15-year lag assumption, the contribution to this worker's cumulative exposure from the 15-year premeasurement period would be identically zero. The difference is thus 33,633 ppt-years, a huge difference in the relative placement of the NIOSH and Hamburg cohort workers on Crump et al.'s cumulative TEQ exposure scale (Crump et al. 2003).

Three of the four Hamburg cohort data points fall more than 4-fold below that for the lowest data point from the NIOSH cohort in both the U.S. EPA's (2000) and my (Starr 2001) meta-analyses, but the two lowest NIOSH cohort data points from Crump et al.'s (2003) meta-analysis are lower than all of the remaining data points used in their meta-analysis. Although Crump et al. (2003) speculated that "results based on cumulative exposure lagged 15 years should not differ greatly from those based on unlagged exposure," their selective use of exposure lagged by 15 years only for the NIOSH cohort creates artificial intercohort differences in cumulative TCDD (and TEQ) exposure that are not trivial.

For the BASF cohort of 243 men with 31 cancer deaths (Otto and Zober 1996), the U.S. EPA (2000), Starr (2001), and Crump et al. (2003) all employed SMR data for four categories of total TCDD intake, expressed in micrograms per kilogram of body weight: < 0.1, 0.1–0.99, 1.0–1.99, and ≥ 2.00. Because exposure in this cohort occurred over a very short time after an uncontrolled reactor release on 17 November 1953, the temporal exposure pattern is essentially a pulsatile spike followed by an extended elimination phase. For these data, all three meta-analyses employed a TCDD half-life of 7.0 years, as previously reported by Otto et al. (1993), and unlagged dose metrics. When the 8.7-year half-life and 15-year lag Crump et al. (2003) used for the NIOSH cohort are coupled with the 7.0-year half-life and no lag they used for the BASF cohort, the joint effect is again a substantial downward shift of the NIOSH cohort's data points relative to those from the BASF cohort, on the cumulative exposure scale.

**TCDD or TEQ?** Finally, we come to the critical issue of whether a dose metric based on TEQ is preferable to one based solely on TCDD. TCDD is the only congener to which workers were exposed in the NIOSH subcohort (Steenland et al. 1999, 2001) and the BASF cohort (Otto and Zober 1996) because Steenland et al. had purposefully excluded from their update 727 workers who were exposed not only to TCDD but also to pentachlorophenol due to the latter material's contamination with higher chlorinated dioxins. Furthermore, in the Hamburg cohort (Flesch-Janys et al. 1998), the only one whose workers had any significant occupational exposure to non-TCDD congeners, there is no substantive evidence that TEQ provides a better dose metric than TCDD. Indeed, the evidence is quite to the contrary.

Flesch-Janys et al. (1998) conducted trend tests of all cancer mortality versus either cumulative lipid TCDD concentration above background (SMRs were 124, 134, 134, and 173 in order of increasing exposure) or equivalent TEQ concentration above background (SMRs were 107, 164, 133, and 164 in order of increasing TEQ exposure): only trend versus TCDD was significant (p = 0.01); trend versus TEQ was totally unremarkable (p = 0.48). Flesch-Janys et al. also conducted trend tests on lung, hematopoietic, and lymphoid cancer and mortality from all causes; in none of these cases was there a significant trend with TEQ.

There is thus no compelling evidence in the three occupational cohorts to support Crump et al.'s (2003) selection of TEQ as the basis for a dose metric. Yet Crump et al. concluded from their analysis that "TEQ exposures within roughly 3-fold of current background levels may be carcinogenic." This conclusion is not justified by the data or Crump et al.'s meta-analysis. To legitimately implicate cumulative serum lipid TCDD concentration as a potential cause of increased human cancer mortality, it would be necessary to show that a dose–response analysis using TEQ produced a model with significantly greater explanatory power than one based solely on the TCDD component of exposure. However, Crump et al. do not appear to have explored this possibility.

Had Crump et al. (2003) conducted such an incremental meta-analysis, they would have discovered that a linear model with cumulative TCDD exposure actually fits the three cohort data sets somewhat better than the very same model with cumulative TEQ exposure, although the difference in log-likelihoods for the two models is small. The evidence from these three occupational cohorts thus indicates nothing at all about the human carcinogenicity of non-TCDD congeners, and this evaluation is entirely consistent with the International Agency for Research on Cancer's 1997 assessment of the evidence regarding these substances (McGregor et al. 1998):

Other PCDDs [polychlorinated dibenzop-dioxins] are not classifiable as to their carcinogenicity to humans (group 3). Dibenzop-dioxin is not classifiable as to its carcinogenicity to humans (group 3). PCDFs [polychlorinated dibenzofurans] are not classifiable as to their carcinogenicity to humans (group 3).

The evidence regarding the potential carcinogenicity of TEQ is simply inadequate.

**A Dose Metric and Dose–Response Model Appropriate for TCDD**

The dose–response models used by the U.S. EPA (2000), Starr (2001), and Crump et al. (2003), in their meta-analyses relate increments in cancer mortality to the various dose metrics discussed previously in proportional fashion, that is, linearly, consistent with the classical mechanistic concepts (e.g., Whitemore and Keller 1978) of how direct-acting carcinogens operate. Such models are predicated on the assumption that the carcinogenic moieties interact biochemically with the DNA of susceptible cells to cause irreversible and cumulative DNA damage that accrues through time, leading eventually to the production of initiated cells and, ultimately, to malignancy. However, this model is not an appropriate one for TCDD.

The wealth of data collected on the carcinogenicity of TCDD in laboratory animals points compellingly toward a promotional mechanism of action, whereby cells previously initiated, either spontaneously or by exposure to direct-acting carcinogens, are conferred a selective growth advantage by subsequent exposure to the "promoting" agent, thereby inducing a rapid and sustained clonal expansion of the initiated cell population (e.g., Berenblum and Shubik 1947; Emmelot and Scherer 1980; Farber 1982). One hallmark of substances classified as "promoters" is the absence of DNA reactivity and mutagenicity in short term in vitro test systems, and this has been demonstrated for TCDD (U.S. EPA 2000). Another is the requirement for sustained exposure to the promoting agent to maintain the selective growth advantage of the initiated cell population for an extended time. For example, early cessation of exposure to phenobarbitol has been shown to result in the spontaneous regression of preneoplastic lesions induced by the direct-acting carcinogen 3'-nitrosomorpholine (Bursch et al. 1984).

A third hallmark of promoters is that the "promoting" exposure must occur after the direct-acting carcinogen exposures. Prior exposures to promoting agents are simply not effective at enhancing carcinogenesis, and a delay or lag between the initiating exposures and subsequent promoting exposures may attenuate the promotional effect, but it is not eliminated. This characteristic of promoters has also been demonstrated with phenobarbitol: only 20% fewer altered hepatic foci were produced when the time interval between initiation by diethylnitrosamine and the onset of a 6-month period of promotion by phenobarbitol was increased from 1 day to 11 months.
Xu et al. 1990). The most recently occurring exposures to promoting agents therefore appear to be the most important ones. Finally, it is worth nothing that the U.S. EPA’s Science Advisory Board Dioxin Reassessment Review Committee called attention to the fact that TCDD appeared to be a promoter and would therefore require a different kind of dose–response model that reflected the unique mechanistic properties of a promoter (Paustenbach 2002; U.S. EPA 2001).

In the present context, a dose–response model appropriate for TCDD would of necessity require both direct-acting carcinogen and promoting components and a corresponding multidimensional dose metric. The promoting component of the model would depend on TCDD concentration, and the direct-acting carcinogen component would need to accurately reflect workers’ previous exposures to multiple direct-acting carcinogens in the workplace as well as elsewhere. Sadly, little attention has been paid to this multiple exposure problem despite its high rate of occurrence in occupational cohorts.

For example, there is clear evidence of exposure to 4-aminobiphenyl in the NIOSH cohort (Collins et al. 1992), and to tobacco smoke in the NIOSH (Fingerhut et al. 1991) and BASF (Ott and Zober 1996) cohorts. None of the meta-analyses discussed herein accounted explicitly for the potential effects of such exposures on all cancer mortality. Indeed, in most of the studies discussed herein (Flesch-Janys et al. 1998; Ott and Zober 1996; Steenland et al. 1999, 2001; U.S. EPA 2000), all of the excess cancer mortality reported in the three occupational cohorts has been attributed to the workers’ TCDD (or TEQ) exposures. Only Crump et al.’s (2003) and my (Starr 2001) meta-analyses included a variable intercept term that allows for increased all-cancer mortality even in the absence of exposure to dioxin-like compounds. Commenting on the 32% increase in baseline all-cancer mortality reported in my meta-analysis, I (Starr 2001) stated that the challenge is to discover the true cause of this significant excess in all cancer mortality, as it appears to be attributable to factors other than the workers’ TCDD body burdens.

The direct-acting carcinogen and promoting components of a dose–response model appropriate for TCDD would also need to be weighted differentially in time; that is, TCDD exposures preceding direct-acting carcinogen exposures would have little or no impact on the likelihood of carcinogenicity, whereas subsequent, and even the most recent, TCDD exposures would need to figure prominently in quantifying the impact of TCDD on carcinogenesis. This latter property of a promoter, namely, that the most recent exposures are possibly the most important (e.g. Xu et al. 1990), is completely at odds with Steenland et al.’s decision (Steenland et al. 1999, 2001), embraced subsequently by Crump et al. (2003), to assign zero weight to the NIOSH cohort workers’ most recent 15 years of TCDD exposure via their 15-year lag assumption.

Finally, the direct-acting carcinogen and promoting components of this dose–response model would have to be multiplicative; that is, risk would be proportional to the product of these two components, so that carcinogenicity would not be predicted unless there were appropriately sequenced exposures of sufficient intensity and duration to both direct-acting carcinogens and TCDD.

Conclusion

In their concluding remarks, Crump et al. (2003) commented that they do not see a clear choice between results from their meta-analysis and the considerably more conservative NIOSH subcohort analysis by Steenland et al. (2001), and suggested that additional research might be warranted if the policy implications of the predicted risks are large. I agree that additional research on the potential carcinogenicity of human exposures to TCDD and other dioxin-like compounds is warranted, but only if detailed exposure data for individual workers are made available to all interested parties and the scope of the research is enlarged to consider both a) exposure to direct-acting carcinogens as well as TCDD and b) dose–response models that are mechanistically appropriate for a promoter such as TCDD.

Without detailed exposure histories for individual workers, it is not possible to assess objectively whether Steenland et al.’s (2001) sophisticated TCDD exposure reconstruction is in any way superior to Fingerhut et al.’s (1991) much simpler dose metric of TCDD exposure duration. As noted above for the workers from the NIOSH cohort with measured serum concentrations, exposure duration appears actually to be somewhat more tightly correlated with the measured TCDD levels than is Steenland et al.’s (2001) cumulative TCDD exposure score, but differences due to the additional years of follow-up included in Steenland et al.’s (2001) analysis must also be considered.

Interestingly, when Adami et al. (2000) split out the all-cancer mortality for the 6 additional years of follow-up that had not been included in Fingerhut et al.’s original report (Fingerhut et al. 1991), the all-cancer SMR (108) was not significant and was reduced relative to Fingerhut et al.’s estimate of 115, yet the dose–response appears far stronger in Steenland et al.’s (2001) update analyses than it does in Fingerhut et al.’s report (Fingerhut et al. 1991). Superficially at least, these early and later results appear inconsistent with one another, but I have shown how at least some of the strengthening of the apparent dose response in the more recent reports is artifactual and attributable to Steenland et al.’s (2001) application of a 15-year lag assumption and longer elimination half-life in their analysis of the NIOSH cohort.

We also conclude that Crump et al.’s extrapolation (Crump et al. 2003) from Steenland et al.’s TCDD analyses (Steenland et al. 1999, 2001) to one based on TEQ is unjustified and overreaching because neither the epidemiologic data nor their meta-analysis of it support the inference that TEQ exposures close to background are likely to be carcinogenic to humans (Flesch-Janys et al. 1998; McGregor et al. 1998). Their extrapolation from TCDD to TEQ is especially troubling because it raises unnecessary concerns about the safety of our food supply.

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