THE PRESENCE OF AH-RECEPTOR AGONISTS IN THE DIET: IMPLICATIONS FOR RISK ASSESSMENT AND MANAGEMENT

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Introduction

The United States Environmental Protection Agency (USEPA) recently suggested that dioxin may be much more potent in humans than previously believed, and it appears that the agency will suggest a new 2,3,7,8-TCDD cancer slope factor of approximately 5 x 10^6 $(mg/kg\text{-}day)^{-1}$, an approximately 30-fold increase over the previously proposed value of 156,000 $(mg/kg\text{-}day)^{-1}$. Further, the USEPA has concluded that dioxin-related health effects are probably occurring in the general population, most likely in individuals with high intakes of meat and fish, and that dietary-related increased cancer risks may be higher than 1 in 1000.

These conclusions pose several challenges to those responsible for assessing and managing risk. For example, because the USEPA has never proposed a "safe" dose (i.e., a "reference dose") of dioxin exposure for noncancer effects, estimated "background" doses of PCDD/Fs have often been used by risk managers as a tool to characterize the magnitude of estimated PCDD/F exposure in environmental risk assessments. However, the USEPA's latest conclusion suggests that a finding of "less than background" PCDD/F exposure will no longer necessarily be considered *de minimus*.

USEPA's conclusion also suggests that changes in dietary habits (reduction in meat intake) would have a significant health benefit. However, it is important to acknowledge that there are numerous Ah-receptor agonists in the U.S. diet. These include anthropogenic compounds such as PCDD/Fs, PCBs, PAHs, and numerous other chemical classes, and also naturally occurring compounds such as indole-3-carbinol (I3C) and its metabolites[1]. I3C is found in large amounts in a number of vegetables of the *Brassica* genus (cabbage, cauliflower, and brussel sprouts), and acute Ah-receptor responses can easily be measured in individuals following consumption of these items[2]. The total TEQ dose that any given individual experiences will be a function of the relative doses and potencies of these compounds, which in turn is governed in part by age and dietary preferences.

In this analysis we present estimates of TEQ doses for different chemical classes in the diet. The published literature was reviewed to determine those dietary components which have significant Ah receptor agonist activity and are known to be present in consumed foods. Dietary consumption rates, relative estimates of potency (relative to 2,3,7,8-TCDD), bioavailability estimates, and biological half-lives for these compounds were established or taken from the literature. Adult external dose estimates are presented in terms of daily dose and cumulative area under the curve (for a 30 year exposure). The relative contribution of each chemical class to total TEQ dose is evaluated, and the influence of different dietary preferences (vegetarian vs. meat

consumption) is assessed. In addition, the merits of using "background" PCDD/F dose as an exposure benchmark are discussed, and we address USEPA's conclusion that dietary PCDD/Fs are responsible for a measurable increase in health effects in the general population.

Methods and Materials

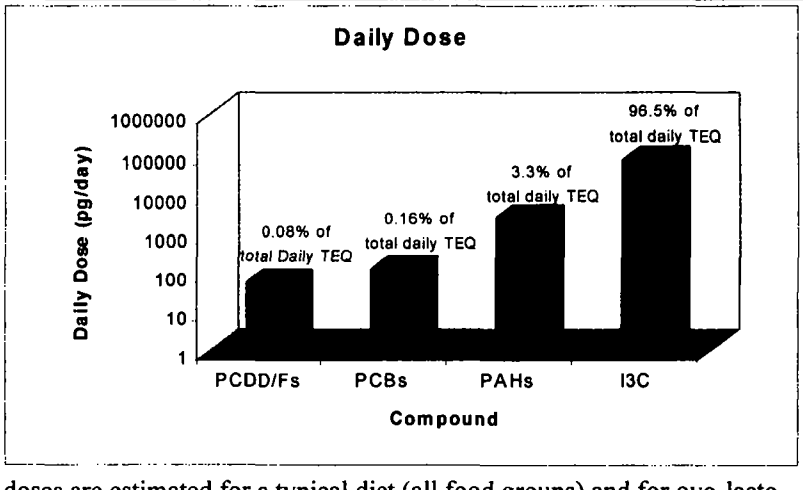
Table 1: Parameters Used for Modeling

Compound	Daily Dose (pg/day)	REP	TEQ daily dose (pg/day)	bioavailability	Half-life
PCDD/Fs	120	----	120	50%	7.5 yrs
PCBs	240	----	240	50%	7.5 yrs
PAHs	$5.0*10^6$	0.001	5000	50%	10 days
I3C	$7.35*10^8$	0.0001	73,500	100%	2 days

Table 1 summarizes the information used to estimate adult daily dose and AUC dose for the following compounds: PCDD/Fs, PCBs, PAHs, and I3C. The daily doses and relative estimates of potency (REP) values were taken primarily from Safe[1]; the REP values are based on antiestrogenic activity as measured in the MCF-7 human breast cell cancer line. Theoretical cancer risks were estimated by multiplying the daily TEQ doses by USEPA's newly proposed 2,3,7,8-TCDD cancer slope factor of $5x10^6$ $(mg/kg\text{-}day)^{-1}$. A 30 year exposure and a body weight of 70 kg was assumed for the cancer risk calculations.

AUC dose was estimated for a 30-year adult exposure, and the daily dose was assumed to be constant throughout the 30 year exposure. Integrated body burden (area under the curve; AUC) was calculated using the exact solution for a one-compartment pharmacokinetic model. Half-lives for PCDD/Fs and PCBs (7.5 years) are USEPA estimates; the half-life for PAHs in humans (10 days) was extrapolated from the half-life for benzo(a)pyrene in rats[3], and the half-life for I3C is assumed to be 48 hours. For the purposes of calculating AUC, the exogenous compounds are assumed to have an oral bioavailability of 50%, based on the measured bioavailability of 2,3,7,8-TCDD[4], while the bioavailability of I3C is assumed to be 100%.

Figure 1: Daily TEQ Dose



The relative contribution of different food groups to daily dietary PCDD/F and PCB TEQ dose was based on a review of the general literature: beef-40%, milk and dairy-40%, fish and chicken-15%, pork-5%. The PAH dose is assumed to be entirely derived from meat; the I3C dose is assumed to be derived entirely from vegetables. Daily TEQ doses are estimated for a typical diet (all food groups) and for ovo-lacto vegetarians (milk and dairy only) and vegans (no meat, milk, or dairy).

Results and Discussion

Figure 1 summarizes the daily antiestrogenic TEQ dose associated with the different chemical classes. I3C clearly comprises a significant majority (over 95%) of the daily TEQ dose, followed by PAHs (3.3%) and PCBs (0.16%). PCDD/Fs contribute the least to the daily TEQ dose (0.08%). Table 2 contains the theoretical increased cancer risks associated with these daily doses, using USEPA's newly proposed cancer slope factor of $5x10^{6}$ $(mg/kg\text{-}day)^{-1}$. The theoretical cancer risk for I3C exceeds unity, while the increased cancer risks for the exogenous compounds range from $1.8x10^{-3}$ (PCDD/Fs) to $7.5x10^{-2}$ (PAHs).

Figure 2: Integrated TEQ Dose for a 30 Year Exposure Duration in Adults

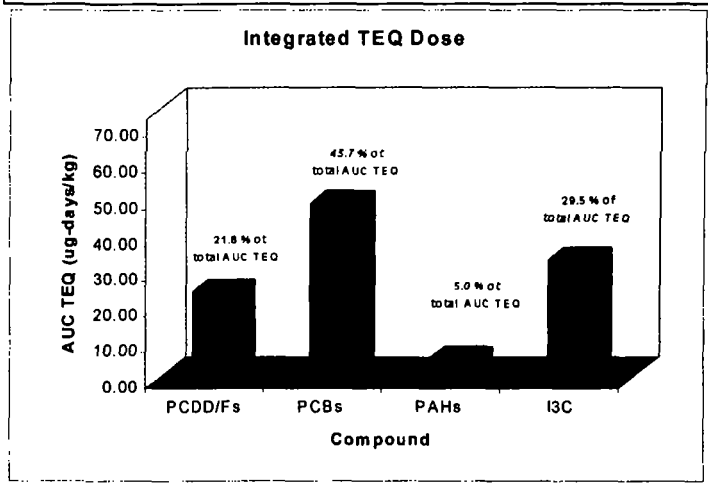
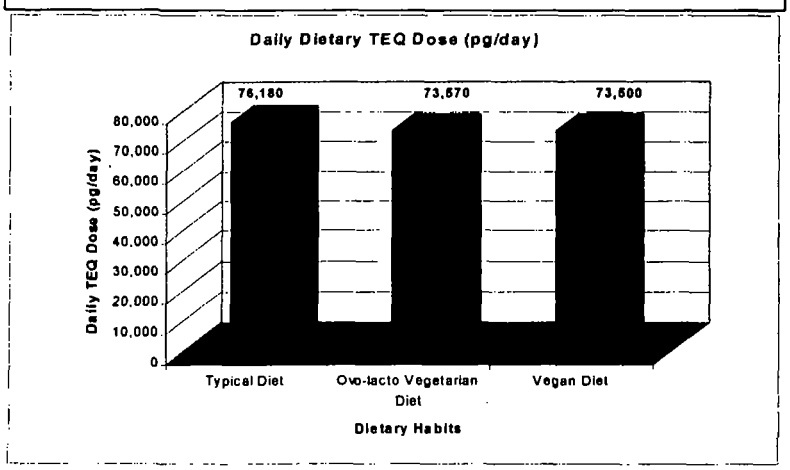


Figure 2 presents the cumulative AUC TEQ dose estimates. Due to the much longer half-lives of PCDD/Fs and PCBs (7.5 years) relative to PAHs (10 days) and I3C (2 days), the relative percent contribution of the chlorinated compounds are much greater than the daily dose estimates in Figure 1. However, even after corrections for bioconcentration, the naturally occurring compounds still contribute a significant fraction to the total absorbed TEQ dose (29.5%).

Figure 3 summarizes the daily doses associated with various diets. The total TEQ dose associated with a typical diet is 76,180 pg TEQ/day. Elimination of all meat from the diet (ovo-lacto vegetarian) decreases the daily TEQ intake to 73,570 pg TEQ/day, while elimination of all meat and all dairy products (vegan) reduces the TEQ intake to 73,500 pg TEQ/day.

Figure 3: Daily Dietary TEQ Dose for Different Dietary Habits



These findings indicate that the USEPA's latest analysis is clearly problematic, for several reasons. First, the results suggest that the use of background or even sub-background PCDD/F doses as a benchmark

of "safe" exposure is no longer tenable. This leaves risk assessors and managers without any means of characterizing noncancer risk in settings where PCDD/F exposure occurs or is expected to occur (e.g., incinerator permitting). Second, the analysis suggests that total elimination of meat and dairy products from the diet would have little to no effect on the daily TEQ dose in the general population. This directly conflicts with recent suggestions that reduction in meat intake would have a measurable health benefit. It also raises questions regarding the cost/benefit of expending millions of dollars to remediate PCDD/F containing soils and sediments. Specifically, if PCDD/F exposures in certain settings are low compared to dietary TEQ intake, source removal may have no significant impact on the daily TEQ dose. Third, the analysis suggests that "dioxin-like" cancer risks in the general population exceed unity, even for those individuals who do not consume meat or milk. This is clearly a counter-intuitive finding.

Table 2: Theoretical increased cancer risks associated with diet

Compound	Dietary Cancer Risk
PCDD/Fs	$1.8*10^{-3}$
PCBs	$3.6*10^{-3}$
PAHs	$7.5*10^{-2}$
I3C	2.2

Overall, the results of our analysis suggest that the newly proposed cancer slope factor for TCDD over-estimates the carcinogenic potential of Ah-receptor agonists. It is worth noting that USEPA's new cancer slope factor is proposed to be based on a single epidemiological study and therefore does not represent a weight of evidence analysis of the numerous other human exposure studies. While we support USEPA's decision to base their analysis on epidemiological, rather than animal data, we suggest that a weight of evidence analysis is required. Such an analysis will provide a more complete set of dose-response data over a broader range of doses (including doses near background). We have prepared an aggregate analysis[5] of three of the largest epidemiology studies on TCDD (which represent a large range of doses), and our findings suggest that a cancer threshold occurs above the current background TCDD exposure levels[5]. We also recommend that comparisons to background TEQ dose be given serious consideration, in a cost/benefit context, when expensive remediation is being considered for the purposes of protecting public health.

References

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