Are Thyroid and Neurodevelopmental Health Effects in North America Related to Rising PBDE Levels?

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Introduction

Exponentially increasing trends in environmental presence of a particular subgroup of brominated flame retardants (BFRs), the polybrominateddiphenylethers (PBDEs), especially in human mother's milk in Canada and the United States (North America (NA)), have been observed [1,2,3]. The toxicological endpoints of concern for PBDEs are similar to those for PCBs and DDT, and are likely to be thyroid hormone disruption, and neurodevelopmental deficits. There are indications that adults, and especially women, are experiencing thyroid disease, particularly hypothyroidism, which appears from the evidence to be increasing in prevalence and incidence in NA, and an apparent growing prevalence of neurodevelopmental deficits in children [4,5,6]. In previous work on this issue, the potential for the increasing body burdens of PBDEs to contribute to this expressed burden of disease was considered together with the trends of other POPs, especially PCBs and DDT [6,7]. In that work, Monte Carlo analysis was used to analyze population distribution co-exposure to trends in human breast milk (lipid) PBDE levels together with estimates of PCB and DDT human milk levels, for 2002, compared to a benchmark PCB level of 1250 ng/g, found to be associated with neurodevelopmental deficits [8]. This overlooked that the Jacobson's cohort exposure was to a complex mixture of contaminants, contained in Great Lakes fish, which included PCBs and DDT, among others, thus disallowing the adding together of these two compounds in that analysis. The aim of this paper is to reexamine this co-exposure analysis using another benchmark of 1650 ng/g total PCB only, found to be associated through postnatal exposure with behavioral impairment in monkeys [9]. Further aims are to report on updated Canadian PBDE milk data, consider estimates of relative potency, and to consider the possible importance of recent evidence on the neurotoxicity of PBDEs in rodents, which provides another benchmark for comparison to the actual distributions, and Monte Carlo simulated future trends, of exposure to these compounds [10].

Methods and Materials

The methods used involve an integrated examination of several lines of evidence, including empirical, toxicological, methodological, and theoretical. The data on milk concentrations, trends, and doubling times from related studies was compiled by literature review, and the relevant data was reviewed and extracted, and subject to summary statistical methods, and then to Monte Carlo (MC) analysis using Crystal Ball (Decisioneering Inc.).The MC analysis combines the probability distributions of several estimated doubling times and reported concentration data of PBDEs as initial conditions, and, assuming a first-order kinetic process, estimates the length of time, from the year 2002, to reach the critical valueof 1250 ng/g, or 1650 ng/g, and the population percentiles in each time estimate [8,9]. Estimates of initial PCB and DDT concentration distributions for 2002 will be introduced as add factors, or constants, first assuming similar potencies for all compounds, and then literature based estimates of different potencies. Synthesis and integration of the data and results are used to critically evaluate the single-chemical and "average" exposure approaches to regulatory risk and health assessments, and the ignoring of existing health conditions in the population.

Results and Discussion

The updated 2002 PBDE data set for Canada is by Ryan, for Ontario, Canada, with arithmetic mean of 125.6 ng/g, median 33.3 ng/g, and standard deviation (SD) of 225.0 ng/g, (range; 0.81 – 956 ng/g) [1]. In this sample, 5% and 2.5% had body burdens of greater than 496 ng/g and 567 ng/g respectively. The second data set (U.S., 2002) was from Schecter et al, with mean of 73.9 ng/g, median of 34.0 ng/g and standard deviation of 103.3 ng/g (range; 6.2 – 418.8) [2]. In this sample, 5% and 2.5% have body burdens of greater than 244 ng/g and 276 ng/g respectively. The third data set (U.S. 2002) is from the Environmental Working Group (EWG), with a mean of 158.75 ng/g and a

standard deviation of 272.75 ng/g (range; 9.0 – 1,078) [3]. In this sample 5% and 2.5% had body burdens of greater than 608 and 694 ng/g respectively. All concentrations are in human breast milk, lipid basis. This data is combined with doubling time estimates from reported trend data (in years: 1.73; 2.00; 2.22; 3.0; 5.0) with mean 2.8 years and standard deviation of 1.3 years [11]. To capture further uncertainty, a global doubling time in humans of 4.9 years with a standard deviation of 0.6 years, and a proxy U.S. doubling time of 3.4 years with a standard deviation of 0.3 years, were used [12, 7].

To estimate PCB and DDT human milk concentration information for 2002, recourse was made to data in several publications, which was then used, with assumptions, to construct a range of estimates [7]. The full explanation cannot be repeated here, so just the estimates will be provided. One estimate of PCBs for Canada/Ontario for 2002 is 103 ng/g, with a SD of 66 ng/g. This implies that 5% and 2.5% would have PCB body burdens of 212 and 232 ng/g respectively. An alternative PCBs level for 2002 is 240 ng/g, with a SD of 154 ng/g. This implies that 5% and 2.5% would have PCB body burdens of 493 and 542 ng/g respectively. If these ranges of PCBs levels are simply added to the similar levels calculated above for the Ryan PBDE data, 5% and 2.5% would have cumulative body burdens of 708-989 ng/g and 799 –1109 ng/g respectively. Assuming the same rates of change over the 1992 to 2002 period as for the PCBs above, yields 2002 mean concentrations for DDT that are basically identical to the PCBs, although for DDT the SD is higher – these are 106 ng/g with SD 103 ng/g, and 246 ng/g with SD of 239 ng/g. This implies that 5% and 2.5% of this sample range would have DDT body burdens of 275-639 ng/g and 308-714 ng/g respectively. If these estimated ranges of DDT 2002 levels were added to the Ryan, PBDE data for 2002, plus the ranges of PCB 2002 levels from above, 5% and 2.5% of the population would have total cumulative body burdens for these three compounds of 983-1628 ng/g and 1107-1823 ng/g, respectively. These PCB and DDT levels are assumed to be constant over the simulation period, although there may be a small ever-decreasing decline towards some positive asymptotic level.

Adding in the PCBs: Equal Potencies and Times to 1250 ng/g from 2002

Simulating these PCB concentration distributions as add factors to the PBDE first order kinetic process yields the selected results for the Ryan Ontario data shown in Table 1.

TABLE 1 – Simulated Times to Critical Value of 1250 ng/g from year 2002 for Addition of PCBs to PBDE (Equal Potency) For Selected Percentiles.

Data Source	T2-yrs	PCB	%-ile	T-yrs to 1250 ng/g
Ryan – mean	2.8	103	5%	-1.7
		103	10%	-0.6
		240	5%	-2.5
		240	10%	-1.4

These results in Table 1 indicate again the significance of considering the distribution of population body burdens rather than just the mean or median. They show that for the higher body burdens of the Ryan data, including the PCBs at either level indicates that the value of 1250 ng/g has already been surpassed prior to 2002 for 5 to 10% of the population. Not shown here, the simulations show similar results for the EWG data with the middle doubling time (3.4 years). Also not shown, for the lower body burdens of the Schecter et al data, simulated at the 3.4-year doubling time, the times to 1250 ng/g range from 2.0 to 3.6 years, from 2002, for 5% to 10% of that population.

Adding in the PCBs and DDT: Equal Potencies and Times to 1650 ng/g

Overlooked in the previous work, the critical value of 1250 ng/g for PCBs drawn from the Jacobson's studies must be taken as based on an exposure to both PCB and DDT (and to some small extent PBDE) as all those compounds, and others, were present in the fish consumed by the mothers in the study cohort. Therefore, we can't add DDT to the PCBs as separately contributing to the critical value of 1250 ng/g. However, we can use another exposure value for PCBs only of 50 ng/g wet weight or 1650 ng/g lipid weight for human breast milk, found to induce behavioral impairments in postnatally exposed monkeys [9].

Simulating these PCB and DDT concentration distributions as add factors to the PBDE first order kinetic process yields the selected results for the Ryan data shown in Table 2.

TABLE 2 – Expected Times to 1650 ng/g from year 2002 for sum of PBDE, PCB, and DDT, for Selected Percentiles – Ryan PBDE Data; Equal Potencies.

PBDE Data Source	T2-yrs	PCB	DDT	%-ile	Yrs to 1650 ng/g
Ryan – mean	2.8	103	106	2.5	-5.9
				5.0	-5.3
				10.0	-4.3
				50.0	0.4
		103	246	2.5	-6.8
				5.0	-6.1
				10.0	-5.2
				50.0	-0.5
		240	246	2.5	-7.6
				5.0	-7.0
				10.0	-6.0
				50.0	-1.3

The results in Table 2 show for selected population percentiles, the expected times from 2002 to the revised critical value of 1650 ng/g. It is apparent, that for the 2.5th, 5th, and 10th population percentiles, this exposure was realized several years in the past. Not shown here, the EWG data show similar results, and there is only one exception in the Schecter et al data.

Accounting for Potencies – Times to 1650 ng/g

It is reported that while exposure to PBDE 99 and PCB 52 individually show similar potencies on a molar basis, co-exposure enhances developmental neurotoxic effects [13]. These synergistic effects have been ignored here for illustrative and simplifying purposes. Since our dose-effect metric keys on PCBs, the relative potency of PCBs is taken to be one (1), and the relative potency of PBDEs from these in vivo studies is calculated as the relative molecular weight of PCB 52 to PBDE 99, which is 292/565 equals 0.52. In vitro studies indicate similar potencies on a molar basis for PBDE 47 and PCB 47 [14]. In this case, the relative potency of the PBDE is 292/486 equals 0.6. The average of 0.56 is used here. There are also reported data that can be used to estimate that DDT is about 30% as potent as PBDE 47 and PCB 47 on a molar basis in the same structure-activity assay measuring increases in protein kinase C (PKC) translocation [15]. Therefore, the potency of DDT relative to PCB was estimated here as 0.30.

The following Table 3 show the results of simulations of times from 2002 to 1650 ng/g adding PBDEs, PCBs and DDT together for the Ontario data and adjusting for relative potency as above. Results for the other two PBDE data sets are not reported here.

TABLE 3: Expected Times to 1650 ng/g from year 2002 for sum of PBDE, PCB, and DDT, for Selected Percentiles, Ryan PBDE Data; Includes potencies.

PBDE Data Source	T2-yrs	PCB	DDT	%-ile	Yrs to 1650 ng/g
Ryan et al – mean	2.8	103	106	2.5	0.5
				5.0	1.6
				10.0	3.1
				50.0	10.8
		240	106	2.5	-0.4
				5.0	0.7
				10.0	2.2
				50.0	10.0
		240	246	2.5	-0.6
				5.0	0.5
				10.0	1.9
				50.0	9.8

These simulation results in Table 3 show that, even allowing for one measure of relative potency, 2.5% of the population is above the 1650 ng/g level, or very near that level as of 2002. It also shows that 5% of the population was very near that level, being just 0.5 to 1.6 years short, and that 10% were just 2 to 3 years from that level based on the trends. Given that the data are for 2002, and the doubling time based on trends for the PBDEs is 2.8 years, the proportions which have reached or are near 1650 ng/g are likely even higher at present.

Conclusions and Recommendations

The data presented here support the need in regulatory safety and health assessments to move beyond the focus on the average or median body burden, to account for the population distribution of the concentrations, and the percentiles in the tails of the distribution, particularly the high exposure portion. This will move such assessments into the real world, and cannot be stated too strongly. The analysis and literature findings suggest that given the present trends for PBDEs, even looked at in isolation, the most highly exposed members of the North American population, including Ontario-Canada, across Canada, and the United States, could already be exposed to toxicologically relevant concentrations of PBDEs based on recent rodent evidence. This initial conclusion is supported by the recent findings where hyperactivity and decreased sperm counts were induced in rat offspring at a dose (single dose on GD6 of 60 ug/kg or 300 ug/kg) of PBDE-99 not much different than those experienced presently by some of the human population with the highest exposures and body burdens of total PBDEs [10]. Based on assumptions in that study, these two doses correspond to human milk lipid concentrations of 429 ng/g and 2143 ng/g respectively, both of which induced the noted effects in the offspring. As well, a significant proportion (2.5% – 5%) could be exposed to such relevant concentrations in as little as 3 to 4 years from 2002 based on a critical value of 1250 ng/g lipid in human breast milk, as per the Jacobson's findings.

Furthermore, even if a measure of relative potency, like the one estimated above, is factored in, and a critical concentration of 1650 ng/g is chosen, for the highest exposed percentiles, any of the summed combinations of the ranges of PBDEs, PCBs and DDT results in no margin of safety, as of 2002, in a time frame of between minus 0.6 years to 1.9 years for 2.5%, and between 0.5 years and 3.0 years for 5% (Table 3, and other data not reported). Based on the PBDE trends, these times have been reached as of now, 2005.

Adding the known body burdens of PBBs, PCDDs, PCDFs, mercury and lead, perchlorate and perfluorinated compounds, and bisphenol A, among many other substances, ups the odds of injury and clinical expression of disease further, and underlines the point. Overall, this study shows that since chemicals don't exist in splendid isolation, taking an initial account of just two of the cumulative past and current body burdens of other compounds with similar toxicological pathways and effects, which by pharmacological definition constitutes an additive effect at least, greatly worsens the situation based on human and animal exposure-effect evidence. Notwithstanding this,

each of these compounds is assessed for health and safety in isolation from the others.

Finally, it is not scientifically valid to ignore the real world and make pronouncements of chemical "safety" based on the assumptions that people are only exposed to the one chemical at a time, and to no others, and do not exhibit a clinically expressed prevalence of a condition that may be related to the toxicity of the chemicals being assessed. If there is such an existing condition, then the idea that a threshold or low dose exists below which no effect will be induced conflicts with the reality of an ongoing disease process that will be added to. Pharmacologically, these are false premises that are not tolerated in medical science, where drug interactions, and existing health conditions are a given, and should not be tolerated any longer in environmental health science.

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