# Is There a Relationship Between the Rise in Thyroid and Neurodevelopmentsl Health Effects in North America and the Rise in Concentrations of PBDEs in the Environment?- An Update

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**Introduction**

In a previous paper on this question, data on an apparently rising prevalence of hypothyroidism, and neurodevelopmental deficits in children was presented. [1] In this context, the issue of the potential for the observed, exponentially increasing levels of PBDEs in the environment to contribute to this expressed clinical burden of disease was raised. [2,3,4,5] This potential contribution was raised because of evidence that the toxicological endpoints of concern for PBDEs include thyroid hormone disruption and neurodevelopmental deficits, and are similar to those seen earlier for PCBs, and DDT. As well, structural and toxicological similarities to PBBs, PCDDs, PCDFs are also part of the concern.

Also raised as issues for further research were two things. First, there is a need in risk assessment to move beyond the focus on the average or median body burden, tissue or human milk concentrations, to account for the population distribution of the concentrations, and the percentiles in the tails of the distribution, particularly the high exposure portion. Second, interactions and additive exposures to and effects of the above mentioned, and other compounds or substances, (e.g. perchlorate, mercury, lead) need to be considered when talking about the "safety" of individual compounds. There is an unfilled need to account for the cumulative past and current exposures and body burdens of other compounds with similar toxicological pathways and effects. We have to deal with the entire environmental exposure, rather than single chemical exposures.

Finally, there is emerging evidence showing the significant influence of genetic polymorphisms, and marked variability in individual vulnerability, and this should be factored in as well before any general judgment is made about risk or product safety.

The aim of this paper is to examine - using Monte Carlo methods applied to the reported human milk (lipid weight) concentrations - the probability distributions, and the population percentiles, of the times required for PBDEs to reach a critical value of 1250 ng/g found by the Jacobsons, [6] for PCBs, to be associated with learning impairments, intellectual deficits, and IQ loss in the offspring. In addition, historical body burdens of PCBs and DDT will be taken from the literature, and using estimates derived here of the distribution of the 2002 human milk levels of these compounds, the

times required for PBDEs, plus PCBs and DDT, to reach 1250 ng/g will be simulated. Finally, note will be made of possibly interacting genetic polymorphisms and variability in individual susceptibility, as well as recent evidence on the toxicology.

**Methods and Materials**

The methods used involve the 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 reviewed and extracted, and subject to Monte Carlo analysis using Crystal Ball (Decisioneering Inc.). The 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 to reach the critical value of 1250 ng/g (1000 ng/g), and the population percentiles in each time estimate. Estimates of initial PCB and DDT concentration distributions will be introduced as add factors, or constants, and assuming similar potencies for all compounds. All distributions are assumed to be normal, and although environmental data tend to be log-normal, particularly for small samples that distribution generates biased estimates of the arithmetic measures of central tendency.

**Results and Discussion**

The first PBDE data set analyzed is by Ryan, et al,[2] with arithmetic mean of 43 ng/g and standard deviation of 62 ng/g, (range; 0.9 – 281.9) combined with doubling time estimates from data reported in references 6 and 7 (in years: 1.73; 2.00; 2.22; 3.0; 5.0) with mean 2.8 years and standard deviation of 1.3 years. Note that the Ryan, et al, reported data trend itself had doubling times of 2 years for the mean levels and 3 years for the median.

**TABLE 1: Forecast: RYAN TIME TO 1250 ng/g at T2 ~ 2.8**

| Percentile | Value | Percentile | Value |
|---|---|---|---|
| 0% | 4.3 | 50% | 13.8 |
| 10% | 8.3 | 60% | 15.3 |
| 20% | 9.8 | 70% | 17.1 |
| 30% | 11.1 | 80% | 19.6 |
| 40% | 12.4 | 90% | 23.8 |
| | | 100% | 78.4 |

The main issue of focus in this Table 1 shows that 10% of the population, reflecting the higher exposed subgroups, could reach the critical value of 1250 ng/g in about 8 years, and 20% in about 10 years.

The second data set was from Schecter, et al [3] with mean of 73.9 ng/g and standard deviation of 103.3 ng/g (range; 6.2 – 418.8). The same doubling time distribution was used. Note that Schecter et al, does not report on any trends.

**TABLE 2: Forecast: SCHECTER TIME TO 1250 ng/g at T2 ~ 2.8**

| Percentile | Value | Percentile | Value |
|---|---|---|---|
| 0% | 3.0 | 60% | 12.6 |
| 10% | 6.5 | 70% | 14.2 |
| 20% | 7.8 | 80% | 16.3 |
| 30% | 8.9 | 90% | 19.7 |
| 40% | 10.0 | 100% | 46.7 |
| 50% | 11.2 | | |

In Table 2 the results indicate a significant lowering of the time for those in the highest exposed groups to reach 1250 ng/g – 6.5 years for the 10% and almost 8 years for the 20%.

The third data set is from the Environmental Working Group, [4] with a mean of 158.75 ng/g and a standard deviation of 272.75 ng/g (range; 9.0 – 1,078). Again, the same doubling time was used. Note also that no trends were reported. The results in Table 3 reflect the higher concentrations reported by the EWG report. Here we see that the highest exposed 10% of the population could reach the critical concentration in just over 3 years and 20% in just over 4 years.

**TABLE 3: Forecast: EWG TIME TO 1250 ng/g at T2 ~ 2.8**

| Percentile | Value | Percentile | Value |
|---|---|---|---|
| 0% | 0.5 | 60% | 8.2 |
| 10% | 3.3 | 70% | 9.6 |
| 20% | 4.3 | 80% | 11.6 |
| 30% | 5.2 | 90% | 14.8 |
| 40% | 6.1 | 100% | 42.6 |
| 50% | 7.1 | | |

In order to capture some further uncertainty in the doubling times, as for example reported by Hites, [5] other simulations were done. Hites reported a global meta-analysis of concentrations and estimated a global doubling time in humans of 4.9 years with a standard deviation of 0.6 years.

However, he also reported that the North America data were always above the regression line – in recent years by a factor greater than 10. Therefore, other regression data from his report on Great Lakes herring gull egg concentrations that visually seemed for present purposes a reasonable fit to the North American trend data he reported was used. This data had a doubling time of 3.4 years and a standard deviation of 0.3 years.

As shown in Table 4, increasing the doubling time increases the time for the 20% most exposed of the EWG population to reach 1250 ng/g in 7 years. 10% of this group could reach this concentration in 5.5 years.

**TABLE 4: Forecast: EWG TIME TO 1250 ng/g at T2 ~ 4.9**

| Percentile | Value | Percentile | Value |
|---|---|---|---|
| 0% | 1.0 | 60% | 12.5 |
| 10% | 5.5 | 70% | 14.4 |
| 20% | 7.0 | 80% | 17.2 |
| 30% | 8.4 | 90% | 21.5 |
| 40% | 9.6 | 100% | 46.6 |
| 50% | 11.0 | | |

Simulating the 3.4 year doubling time yields times for the EWG sample of 3.9 years for the 10% most exposed, and 5 years for the 20%, to reach 1250 ng/g.

**Adding in the PCBs**

Generally overlooked in risk assessment of PBDES, and in general, are the interactions and additive exposures of compounds or substances with similar toxicological pathways and effects. The evidence indicates that PCBs are one important example of this omission. Data on human milk fat concentrations of PCBs for Ontario, Canada, for example show that high and significant exposure occurred in the past.[7, 8] In 1971/72 the mean concentration was 1200 ng/g, with range 200 to 3000 ng/g. In 1973/74 the mean was still 1200 ng/g, with range 100 to 2500 ng/g. In Michigan, in 1977/78 the mean was 1496 ng/g, with a range of 300 to 5100 ng/g.

From 1975 to 1985 the mean for Ontario did not vary significantly, grand averaging about 765 ng/g, with a coefficient of variation (COV) (standard deviation (SD) divided by the mean) that grand averaged 0.64, implying a grand average SD of 490 ng/g. In Ontario in 1992, reported mean concentrations were 220 (maximum 612) to 272 (maximum 1042) ng/g. For Canada as a whole in 1992, mean concentrations of 223 (maximum 979) and 238 (no maximum cited) ng/g were reported. The 1992 grand mean for all this Ontario and Canada data is about 240 ng/g.

To estimate concentration information for 2002, recourse was made to data in several publications, which was then used, with assumptions, to construct estimates. In Sjodin, et al, [9] data showed that the concentration of PCB 153 in human serum (lipids) from the United States declined from 71 ng/g in 1992, to an average, over 5 sample pools from various areas, of almost 31 ng/g, or by about 57%. Applying this decline to the grand mean of 240 ng/g for Canada/Ontario yields an estimate for 2002 of 103 ng/g. Applying the derived above estimate of the COV of 0.64 yields a corresponding SD of 66 ng/g.

Alternatively, data in Manchester- Neesvig, et al, [10] showed no decline in total PCB concentrations in Lake Michigan sediments over the period 1992 to 2002. From 1985 to 1992 there was about a 57% decline. Applying this zero decline factor yields a 2002 mean estimate that is the same as the 1992 one, which is 240 ng/g, and using the COV of 0.64, yields an estimate of the SD of 154 ng/g.

Simulating these two PCB concentration distributions as add factors to the PBDE first order kinetic process yields the following selected results shown in Table 5.

| TABLE 5 Data Source | T2-yrs | PCB | Percentile | T-yrs to 1250 ng/g |
|---|---|---|---|---|
| Ryan – mean | 2.8 | 103 | 5% | 2.7 |
| | | 103 | 10% | 3.8 |
| | | 240 | 5% | 1.9 |
| | | 240 | 10% | 3.0 |
| Schecter – mean | 3.4 | 103 | 5% | 2.9 |
| | | 103 | 10% | 3.6 |
| | | 240 | 5% | 2.0 |
| | | 240 | 10% | 2.8 |
| EWG – mean | 3.4 | 103 | 5% | - 1.6 |
| | | 103 | 10% | -0.8 |
| | | 240 | 5% | -2.4 |
| | | 240 | 10% | -1.6 |

These results 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 EWG data set, with the middle doubling time drawn from the Hites data, including the PCBs at either level indicates that the value of 1250 ng/g has already been surpassed for 5 to 10% of the population.

**Adding in the DDT**

There was limited data reviewed here to support a similar potency for DDT, however, Eriksson and co-workers [11] have reported that low dose exposure to PCBs and DDT during a critical period in neonatal mice can lead to disruption of adult brain function and increased susceptibility to toxic agents as adults. They also report that co-exposure to PBDE 99 and PCB 52 enhances developmental neurotoxic effects. Given this and other evidence of concern about DDT not cited here, it was assumed for an initial effort that DDT would be additive in the same metric. In the future, given better information, variability in potency can be simulated.

In the past, exposures and body burdens of DDT were very high. [7, 8] In Ontario, in 1967/68 the mean human milk fat concentration was 5399 ng/g, with a range of 1850 to 17280 ng/g. In 1969/70 the mean was 3480ng/g, with range 110 to 11400 ng/g. The levels did not start to drop till the middle 1970s, after DDT use was restricted. From 1975 to 1985 the levels did not decrease significantly, showing a grand mean of 6 observations of 732 ng/g and a grand mean COV of 0.97. For 1992, four data sets were found reported, two for Canada (247 ng/g; 232 ng/g), one for Ontario (205 ng/g), and one for the Great Lakes Basin (298 ng/g) residents only. The grand mean was 246 ng/g.

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.

In the results below in Table 6, adding in the DDT distribution on top of the PCB distribution produces some very interesting increases in the population percentiles already exposed to the critical value of 1250 ng/g, and sometimes this exposure was realized several years in the past. These results show for selected combinations of PCBs and DDT, and doubling times, what maximum percentile is already at that value. Because the PCB and DDT mean concentrations are

almost identical, the reverse combinations are omitted, as the result values are not statistically different. Also included are the time values for the 10th percentile for all combinations. This shows that at least 10% of the population samples are always at or above 1250 ng/g, and that this body burden may have been reached significantly in the past. These percentiles (and higher ones as well) are more vulnerable to increases in PBDE or other toxic substance exposures.

**TABLE 6**

| PBDE Data Source | T2-yrs | PCB | DDT | %-ile | Years to 1250 ng/g |
|---|---|---|---|---|---|
| Ryan et al – mean | 2.8 | 103 | 106 | 15(10) | -0.2 (-1.0) |
| | | 103 | 246 | 20(10) | -0.3 (-1.9) |
| | | 240 | 246 | 25(10) | -0.4 (-2.7) |
| Schecter et al – mean | 3.4 | 103 | 106 | 15(10) | -0.5 (-1.1) |
| | | 103 | 246 | 25(10) | -0.3 (-1.9) |
| | | 240 | 246 | 35(10) | -0.2 (-2.8) |
| EWG - mean | 4.9 | 103 | 106 | 35(10) | -0.1 (-3.8) |
| | | 103 | 246 | 40(10) | -0.3 (-4.7) |
| | | 240 | 246 | 45(10) | -0.5 (-5.5) |

**Other Issues**

There is evidence that individual susceptibility can vary markedly, and that averages can conceal this. The Jacobsons found that while 60% of the most heavily exposed children (1250 ng/g and above) did not show a poor performance at the bottom 15th percentile of the IQ test, fully 40%, a substantial minority, appear to be at risk for a functionally significant deficit.[12] Another paper shows that certain genetic polymorphisms predispose the effects of PCBs and PCDFs on arthritis and chloracne, resulting in odds ratio 95% confidence intervals of 1.2 to 8.1, and 1.0 to 3.4 respectively. Also identified were increased susceptibilities to certain cancers.[13] A study on the physiological role of the aryl hydrocarbon receptor revealed pronounced intra- and inter-individual variations, up to 25-fold, in CYB1B1 expression.[14] Other evidence shows that PCBs and PBDEs perturb intracellular signaling processes critical for nervous system development, learning, and memory, and that both compounds alter these pathways with equal potency and efficacy on a molar basis.[15] There is also evidence of additive effects of PCBs and methyl mercury on cognitive, motor and auditory deficits during early development. [16]

**Conclusions**

The data presented here support the need in risk assessment 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. The analysis suggests that given the present trends for PBDEs, even looked at in isolation, a proportion of the North American population could already be exposed to toxicologically relevant concentrations of PBDEs, or in as little as 3 or so years.

However, 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 greatly worsens the situation. Given the knowledge we have now about their multiple mechanisms of action, suggests that past high exposures to PCBs [17] and DDT increased the probability of, and contributed to, the historical and current burden of clinically expressed

hypothyroidism, and neurodevelopmental deficits in children. Even a range of current body burdens of PCBs and DDT, added on top of the current trends in PBDEs suggests that a significant proportion of the population is now exposed to levels that may cause such effects, particularly in susceptible individuals. Adding the known burdens of PBBs, PCDDs, PCDFs, [18] mercury, and lead, among other substances, ups the odds of clinical expression further, and underlines the point.

This data suggests that taking account of even just two more of the many chemicals that people are exposed to, and allowing for the statistical distribution of exposure and body burden, more or less completely removes any margin of safety that exists for a significant proportion of the population, for exposure to additional substances like brominated flame retardants.

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