SINGLE CHEMICAL RISK ASSESSMENTS ARE NOT PROTECTIVE OF HEALTH – THYROID AND NEURODEVELOPMENTAL CONTEXTS

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Introduction

In previous work on this issue, the potential for increasing body burdens of PBDEs to contribute to an expressed burden of thyroid and neurodevelopmental disease was considered together with the trends of other POPs, especially PCBs and DDT [1,2.] 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 molar-based potency estimates of PCB and DDT human milk levels, for 2002, compared to benchmark total PCB levels of 1250 ng/g, and 1650 ng/g found to be associated with neurodevelopmental deficits in human offspring (prenatal) and monkeys (postnatal), respectively . It was concluded that the addition of PCBs and DDT only to the PBDEs resulted in there being no margin of safety remaining for any further exposure to POPs, such as related brominated flame retardants, for 2.5 to 5% of the exposed population. Issues were raised concerning factors that need to be considered before anyone declares chemical exposures safe. These factors needing consideration include: trends and distribution of exposures/body burdens, not just mean or median; co-exposure to other chemicals and their interactions; existing health conditions in the exposed population; and whether the appropriate life stage and sensitivity is being examined. Subsequent work has found *in vitro* and *in vivo* evidence of additive to synergistic effects of complex chemical mixtures on estrogenic, [3] thyroid hormone [4] and neurodevelopmental [5] endpoints, as well as data on structure-activity relations, [6] pharmacokinetic parameters, [7,8] and an additional PBDE benchmark for neurotoxicity in rodents [9], all of which are pertinent to the sensitivity of the fetal and infant life stages. Additional evidence on the prevalence of thyroid disease and possible associations with industrial chemicals is also located. The aim of this paper is to review this evidence in the context of the previous work, the risk assessment methodological and policy issues raised there, and to provide additional perspectives on, and risk probabilities of, possible health effects of industrial chemicals.

Materials and Methods

The methods used involve an integrated examination of several lines of evidence, including empirical, toxicological, methodological, and theoretical. The statistical and data generation methods were described previously. The relevant additional evidence and data is synthesized and presented in a logical and integrated manner, and together with analytical results is used to critically evaluate the single-chemical and "average" exposure approaches to regulatory risk and health assessments, and the ignoring of the other issues and factors deemed essential here to consider before declaring chemical exposures safe.

Results and Discussion

Additional Evidence on Existing Thyroid and Neurodevelopmental Health Conditions

Limited data on hypothyroidism prevalence in Ontario, Canada was previously provided [1,2]. Additional data show that in Ontario, the number of cases increased almost 4-fold over the period 1980 to 2000, or 7.5 % average per year. The age and sex standardized morbidity rate for Ontario increased from 53.4 cases per 100,000, to almost 129 cases per 100,000, an increase of 141% over the period 1980 to 2000. Additional studies show an association between human thyroid health morbidity (which includes hypothyroidism) and residence in Great Lakes Areas of Concern (AOCs), designated by the International Joint Commission as being more or less highly polluted environments. Human females in the St. Clair River AOC, which is the location of Canada's Chemical Valley, containing a concentration of petro-chemical industry, had thyroid disease Standard Morbidity Rates (SMRs) 1.37 to 4.16 times the Ontario average measured over the years 1985 to 1988 [10]. In the Detroit River - Windsor AOC, female thyroid disorders were 24% greater than the Ontario average over the same time period. Also in Windsor, the onset between birth and age 24 was 208% of the Ontario average. The morbidity was elevated across all age categories. Carpenter et al, [11] found a significant, so-called "striking" elevation in thyroid disease SMRs, presented as hospital diagnoses,

in females resident within 15 miles of 6 New York State AOCs, compared to control groups from 3 residence locations not so situated. These elevations occurred in all ages greater than 25 years, although the age 20 to 24 group was elevated but not significantly. The incidence and difference increased with age. As well, Carpenter et al, [12] showed highly significant elevations in SMRs (about 20%) for thyroid disease in females at all ages greater than 20 years, resident in New York zip codes containing or abutting hazardous waste sites containing persistent organic pollutants (POPs) compared to zip codes with sites without POPs, and to sites that do not contain hazardous waste sites. The use of medication used to treat hypothyroidism continues to increase exponentially as previously reported. In Great Lakes fish and wildlife, severe elevations in thyroid disease have been observed, especially in the Detroit River and western Lake Erie [13]. There is evidence of neurodevelopmental and behavioral impairment. Herring Gulls and Salmon showed severe thyroid pathology. In experiments, rats fed Great Lakes salmon, which are contaminated with many chemicals, developed thyroid dysfunction compared to controls fed Pacific Ocean salmon. In other studies dosed rats were hyperactive and easily frustrated. [13]

Recent studies continue to report on the growing prevalence of neurodevelopmental disorders in North American children raised in previous work. Colborn [14] points to evidence linking thyroid hormone disruption to this growing prevalence, and possible links to industrial chemicals. Castellano et al, [15] found that children with ADHD have reduced brain volume, particularly the cerebellum, which is disproportionately smaller than other brain parts. The cerebellum is highly sensitive to thyroid hormone insufficiency and is targeted by PCB exposure [16]. PCB exposure alters motor behaviour associated with cerebellar function. In young children, the association between PCB body burden and response-inhibition measures of behaviour is stronger in those children with a smaller corpus callosum, an area of the brain affected by thyroid hormone [16.] Note that PCBs and PBDEs are structural analogs and share certain mechanisms of action on the thyroid system, including inducing a state of relative hypothyroidism [4, 16]. However, Kuriyama et al [9] point also to the disruption of the cholinergic system by PCBs and PBDEs, found by Eriksson and co-workers to be associated with hyperactivity and other neurodevelopmental effects in mice.

Selected Co-exposure Cumulative Effects Evidence

All of these prevalence data, which are unexplained, reflect a background real world exposure to complex mixtures of many chemicals, and many synthetic organic chemicals have toxic effects on the thyroid and nervous systems at several possible targets [16] . Recent papers have reported at least additive to synergistic or enhanced effects of complex mixtures in an estrogenic experimental model [4], and a rat thyroid hormone model [5]. In each model, the individual chemicals in the mixture were all below their NOELs, but the combined mixture showed measurable hormone actions in a dose-response manner. The estrogenic model data confirmed the concentration addition approach, and the thyroid model data confirmed that the additive model was valid for the low doses. Eriksson et al [17] report that while exposure to PBDE 99 and PCB 52 individually show similar potencies on a molar basis, co-exposure enhances developmental neurotoxic effects. There is also in vivo evidence of additive effects of PCBs and methyl mercury on cognitive, motor and auditory deficits during early development [18]. In vitro evidence indicates that co-exposure to PCBs and methyl mercury act synergistically to reduce rat brain dopamine content.[19]

Mechanistic Evidence Affecting Life Stage Sensitivity

Factors that determine the dose at target and subsequent effects include distribution, metabolism, clearance, and plasma transport. There is evidence in mice that the pups excrete PBDE-47 (single dose at PND-10) at a slower rate than the adults. Within 24 hours, only 41% of the dose remained in the body of the adult mice versus 69% in the pups. By the tenth day following exposure, a mere 6% was in the adults yet 34% of the BDE 47 was still in the pups. Doses at PND-22, 28, and 40 all reflected a similar lower clearance by the pups [20]. Consistent with this evidence in mice is one study of breastfed human infants showing PCB concentrations in the blood of the baby approaching 4 times that of the mother and baby at birth after 6 to 9 months. After 2 years of breast-feeding the levels in the baby approached 5 to 6 times higher than at birth [21]. In vitro evidence shows that PCBs, PBDEs, metabolites of these two, other flame retardants and numerous other halogenated phenolic compounds competitively bind to the thyroid hormone plasma transport protein transthyretin, thus selectively accumulating in blood [22] and inhibiting TH transport, which may create toxic effects especially in the fetus and neonate [23]. This effect is compounded by new studies indicating that TH receptors, and thus TH action, are targets of industrial chemicals,

such as PCBs, PBDEs, bisphenol-A, and halogenated derivatives and metabolites of these compounds [16]. Not only might this transthyretin binding result in a TH insufficiency and disrupted receptor signaling, but also provides for the transport of known neurotoxic chemicals into the fetal compartment and brain [24]. This transport, combined with the evidence of possibly lower chemical clearance in babies compared to the adult, and thus higher accumulation, suggests that the dose delivered to the fetal/neonate target organs will be higher than the concentration in the adult would indicate. That is, the concentrations measured as exposure in mother's milk, for example, may be a significant underestimate of the dose accumulated and delivered to critical targets in the offspring. This may be related to the monkey postnatal exposure study benchmark of 1650 ng/g, which, unlike other human and animal studies that found effects to be associated with prenatal exposure, employed tests specifically designed to assess the function of brain structures that develop late, such as the prefrontal cortex, which does not fully mature until well after birth [25, 26] Consistent with this fetal and infant difference from adult pharmacokinetics, Kuriyama et al [9] showed that rats exposed in utero (GD-6) to a single environmentally relevant dose of PBDE-99 (60 and 300 ug/kg body weight) became hyperactive and to have reduced sperm counts. These doses are the lowest doses of PBDE reported to date to have an in vivo toxic effect in rodents – reflecting the fetal sensitivity. The doses are very close to human exposure levels as measured by the highest reported amounts of total PBDE in human breast adipose tissue – 429 ng/g and 2143 ng/g based on assumptions in that study. Other studies support this male reproductive effect in showing that the PBDE mixture, DE-71, and certain specific congeners, are anti-androgenic by several measures, and display competitive inhibition or antagonism of the androgen receptor, with PBDE-100 having a Ki of 1 uM [7].

Risk Assessment Implications

The evidence of increasing prevalence and rate of thyroid disease in Ontario, Canada, and the geographic variations associated with proximity to contaminated sites, indicates that a disease process is underway and on medical and pharmacological grounds needs to be accounted for in any health risk assessment of exposure to the numerous chemicals that have, or may have, thyroid effects. The neurodevelopmental problems in children are also becoming more prevalent and need to be accounted for too.

Using the Monte Carl model [1,2,3] to simulate the times from the year 2002 to 429 ng/g milk lipids level of total PBDEs, based on the observed levels and trends for Ontario in 2002 (mean 125.6 ng/g, SD 225.0 ng/g, doubling time 2.8 years) shows that 5% of the exposed population was already in excess of that level, and that 50% would reach that level in 3 years after 2002. Adding the low level PCBs, as previously calculated, at 103 ng/g, SD 66 ng/g, results in the 429 ng/g level having been reached by 50% about 1 year before 2002. Considering the Ontario PBDE-99 data in isolation, with mean 31.6 ng/g, SD of 72.4 ng/g, minimum of 1.2 ng/g, and maximum of 299.0 ng/g, yields times to 429 ng/g of 3 to 4 years from 2002 for 2.5 to 5.0% of the exposed population. Adding in PCBs at 103 ng/g predicts that 10% of the population reached the 429-ng/g level in the year before 2002, and that 50% would reach that level in less than 4 years. Other total PBDE data for New York City female adipose tissue range from 20-4060 ng/g lipid, with mean 253 ng/g and SD of 639 ng/g [27]. The range of PBDE-99 only was <1 – 1380 ng/g, with mean 74.4-ng/g and median 10.3 ng/g. While not done here, similar Monte Carlo simulations using this data would predict even higher population percentiles and shorter times to the benchmark exposures and body burdens.

If one considers critically the Health Canada human health risk assessment for PBDEs, which found a margin of exposure of 300 one sees the following. The LOEL that was used was single dose 0.8 mg/kg on PND 10 on mice. The Kuriyama et al study found a new LOEL of 0.06-mg/kg single dose, GD 6 of PBDE-99 in rats. This dose is 13.3 times lower, so the MOE is thus divided by this factor = 22.5. The maximum breast milk concentration used by HC was 589 ng/g, whereas the later data for 2002 showed a maximum of 956 ng/g, which is another reduction in the MOE of 1.62, meaning the MOE is now 300/1.62 = 185/13.3 = 14. Accounting for the New York adipose data noted above (at equilibrium all lipid based numbers should be the same), the maximum is 4060 ng/g, which is 4.4 times higher, so the MOE accounting for this dose would be 22.5/6.9 = 3.3. Also, the HC model used an infant weight of 7.5 kg, which was an average calculated for 0-6 months. Accounting for a newborn weight of 3.5 kg ups the dose per kg by 7.5/3.5 = 2.14, so the MOE accounting for this at the highest NY doses is now 3.3/2.14 = 1.54. Using the highest Canadian dose means the MOE is 14/2.14 = 6.6. If you add the additive effects of PCB and DDT body burdens at the high ends (816 ng/g adipose [26] and the 95th percentile 2630 ng/g blood lipid estimate of the CDC,

respectively), shown to act mechanistically to the same downstream neurotoxic endpoint, makes the total body burden 7506 ng/g lipid, bringing the MOE to 1.54/1.85 = 0.83, (or 6.6/6.85 = 0.96 for the Canadian dose MOE), not including default uncertainty factors. Therefore, there is no margin of safety for any further exposure to any compounds and/or metabolites with thyroid or neurotoxicity as a downstream endpoints. This includes Deca-BDE, as it is reactive and likely degrades to more potent PBDEs, and there are large environmental inventories [28].

It is not possible here to further analyze the additional cumulative effects on thyroid and neurodevelopmental health of perchlorate, bisphenol-A, perfluorinated compounds, dioxins, furans, pesticides, mercury, lead, other BFRs, and other compounds recognized to be active on these endpoints. The 3rd CDC body burden report shows that a significant proportion of the population has cumulative body burdens of these compounds that the evidence predicts are contributing to the observed disease burdens.

It is also unfortunate that there are no pharmacokinetic data for most chemicals, and thus no basis for predicting the significance of body burdens from the perspective of hormone receptor binding action and signaling disruption, although a few competitive binding affinities have been estimated, for example, the androgen receptor binding competitive inhibition constant, Ki, for PBDE-100 of 1uM, and a similar IC50 for DE-71 of 5 uM [7]. There are other such estimates relevant to TH receptors and action [16]. While beyond the present scope to analyze these factors, it is noteworthy that the physiological dose-response range for hormone action covers at least 6 orders of magnitude, and the relationship between receptor occupancy and physiological response is non-linear [29]. One important implication is that what are commonly seen as very low body burdens of many chemicals can, individually and cumulatively, add up to induce responses at levels far below those indicated by the Ki or IC50. Work to estimate competitive binding constants for industrial chemicals, and the implications of this data is much needed.

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