Organohalogen Compounds, Volume 61, Pages 195-198 (2003)

IS THERE A RELATIONSHIP BETWEEN THE RISE IN THYROID AND NEURODEVELOPMENTAL HEALTH EFFECTS IN NORTH AMERICA AND THE RISE IN CONCENTRATIONS OF PBDES IN THE ENVIRONMENT?

Tom Muir

* Great Lakes and Corporate Affairs, Environment Canada - Ontario Region, 867 Lakeshore Road, Burlington, Ontario, Canada. L7R 4A6.

Introduction

The brominated flame-retardants are one of many substances used to reduce inherent fire hazards in a variety of commercial applications, such as electronics, plastics, furniture, and textiles. Increasing trends in environmental presence of a particular subgroup of BFRs, the polybrominated diphenyl ethers (PBDEs), especially in human mother's milk, have been referred to as "alarming"[1]. There is evidence of thyroid hormone system interaction and disruption [1]. There is also evidence of learning disabilities induced in mice by PBDEs [2]. In general, while our knowledge of the toxicity of these compounds is limited, what information is available indicates that the toxicological endpoints of concern for environmental levels of PBDEs are similar to those seen earlier for PCBs, and are likely to be thyroid hormone disruption, neurodevelopmental deficits, and cancer [1,2,3]. PBDEs are listed as endocrine disrupting chemicals. There are also indications that adults, and especially women, are experiencing thyroid disease, particularly hypothyroidism, which appears to be endemic in North America [3,4]. In turn, this maternal hypothyroidism is one mechanism by which the fetus and neonate are affected, and which can lead to neurodevelopmental deficits, such as those seen by the Jacobson's [5], and that are reported in other related literature as growing in prevalence in North American (NA) children. Given this, the aim of this paper is to report some data related to the apparently rising prevalence of hypothyroidism, and neurodevelopmental deficits in children, and to raise the issue of the potential for PBDEs in the environment to add to this already expressed clinical burden of disease.

Methods and Materials

The methods used involve the examination of several lines of evidence, including empirical, toxicological, methodological, and theoretical. Selected literature is reviewed to determine the basis of the expressed concern. Standard economic principles and methods are applied to published data on potential costs, and to estimate costs where needed.

Results and Discussion

It appears from the data available that there is an increasing prevalence of hypothyroidism, and child neurodevelopmental deficits, in Canada, and NA, and that this situation is unexplained. Table 1 below describes the number of cases of unspecified hypothyroidism ("any" diagnosis) in Canada, and Ontario (as a subset) for the years 1994 to 2000. This data is provided by the Canadian Institute for Health Information, Toronto, Ontario, from the Hospital Morbidity Database, and captures information on patients separated - through discharge or death - from an acute care facility in Canada. The omission of chronic care facilities may result in slight underestimates of the number of cases.

TABLE 1 Number of Cases of Unspecified Hypothyroidism in Ontario and Canada, 1994 – 2000.

Year	Number of Cases in Ontario	Number of Cases in Canada
1994	12,139	48,709
1995	13,679	53,637
1996	14,836	57,144
1997	14,988	61,789
1998	15,865	70,783
1999	16,585	76,956
2000	17,782	83,837

In Canada, the number of cases grew by 72% in total over the period, or 12% per year. The doubling time is 7.4 years. In Ontario, the total growth was 47% or almost 8% per year, over the same period. In Ontario, over the 1996-1998 period, hospital treatment for hypothyroidism cost an average $591,000 per year or $3,400 per case. In addition, over 1998-1999, doctors were paid almost $8.1 million for treating patients with hypothyroidism in Ontario [4]. In the United States, the American Thyroid Association reports that more than 2% or 5 million Americans have diagnosed hypothyroidism, and up to 17% may have it undiagnosed [6].

Reflecting the increase in hypothyroidism is a large increase in the prescription sales, in Canada, of Synthroid, a product indicated for the treatment of hypothyroidism. Synthroid was the most dispensed medication in Canada in 1999, 2000, and 2001 [7]. Figure 1 below shows the trend in prescription sales of Synthroid in Canada for the period 1985 to 2000 [7]. The exponential shape of the fitted curve is evident, and the doubling time is 6 years. In Canada, the almost 5.4 million prescriptions dispensed in 2000, assuming 50 pills per time, cost, at an estimated $20 to $30 per 100 pills [6,7,8], a total of $54 million to $81 million, plus an estimated $9 dispensing fee per prescription or almost $49 million, for a total of $103 to $130 million per year. In the U.S., 5 million patients purchased 36 million prescriptions and 1,825 million pills [6, 7, 8]. At the same cost of $20 to $30 per 100 pills and the $9 per prescription dispensing fee, the overall annual cost in the U.S. is $365 million to $548 million for pills plus about $324 million for dispensing fees, for a total of $689 million to $872 million.

It is also evident that there is a significant and growing prevalence of neurodevelopment disorders among North American children. There is evidence that the prevalence of autism, hyperactivity, attention deficit hyperactivity disorder (ADHD), learning and behavioral disabilities, and mental retardation, among other afflictions, are widespread amongst children and are growing substantially [4]. For example, it is estimated that 12 million U.S. children under 18 years of age suffer from one or more learning, developmental, or behavioral disabilities, and the real number may be 20 million or more. Another estimate is that ADHD affects 3 to 6% of all school children, although other evidence suggests the prevalence may be as high as 17%. Male children are much more likely to be symptomatic. One Ontario Health Study found that the prevalence of ADHD was 9% in boys and 3% in girls. Within the State of California, the number of children entered into the autism registry increased 210% between 1987 and 1998 (compared to a 60% rise in population). Overall, aggressive behaviour and propensity to violence appear to have increased over the last decade [4.]

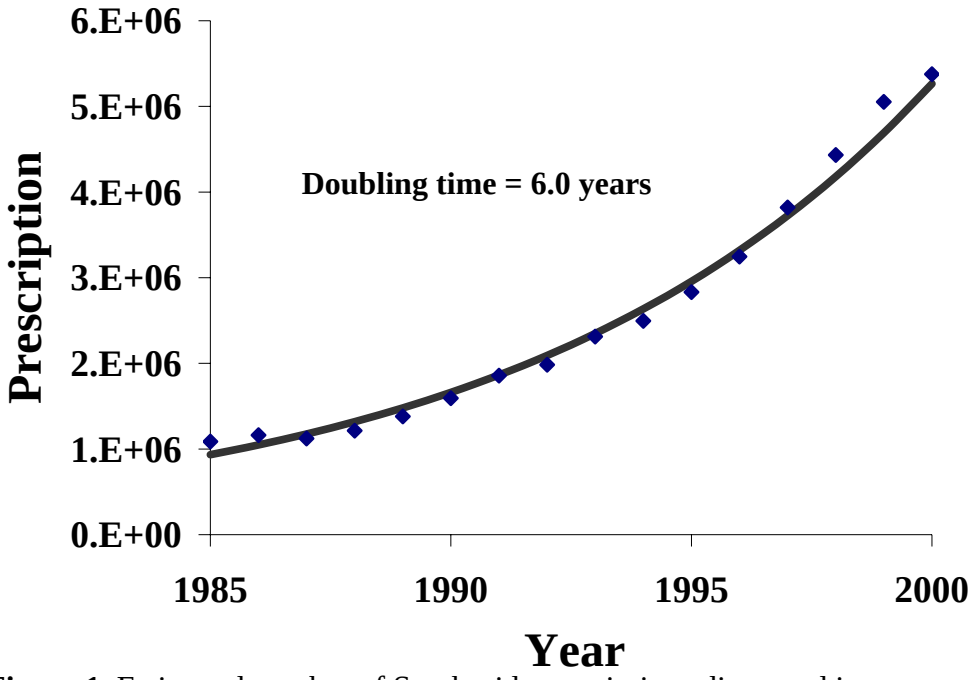

Figure 1. Estimated number of Synthroid prescriptions dispensed in Canadian retail pharmacies(source: IMS Health Canada).

Children with hyperactivity and ADHD are commonly administered the medication Ritalin. The number of Ritalin pills dispensed in Canada more than doubled, from 26.8 million to 56.2 million, from 1994 to 1998 [4]. The cost in 1998 is estimated at $50 million per year. More generally, the number of prescriptions dispensed annually in Canada increased about 400% from 1991 to 2001 [7]. In the U.S. the number of children taking Ritalin has roughly doubled every 4-7 years since 1971 to reach a current estimate of about 1.5 million, although the real total may be 8 million [4]. The cost for the lower number is estimated to be almost $2 billion a year, although this depends on dosage and the number of pills per day (here we assume 4 pills per day at 89 cents each) [4].

The rapidly increasing trends in the level of PBDEs, which are a newly-recognized class of chemicals of concern with potential thyroid and other toxicity as noted above, in biota and humans has become of increasing concern over the last decade, although there is no direct evidence that PBDEs at these levels are contributing causes to the clinical disease burden noted above. In Great Lakes Herring Gull eggs the levels range from 10 to 800 ng/g wet weight, with doubling times of 4 years in Lake Ontario, 3 years in Lake Michigan, and 5 years in Lake Huron. Trend data for total BDEs in human milk (lipid weight) from Ryan et al [9], for Vancouver, Canada show median level increases from 0.7ng/g in 1986 to 1.7 ng/g in 1992, to 25.4 ng/g in 2002. Doubling time is 3 years. Increases in the mean level are from 0.6 ng/g in 1986 to 4.7 ng/g in 1992 to 42.8 in 2002. Doubling time is 2 years. Note that the 1992 Vancouver mean level of 4.7

ng/g compares to an overall Canadian concentration of 15.0 ng/g for the same year, a 3.2-fold difference. While current environmental levels may still offer a margin of safety for the mean exposure to PBDE from food, say for adults, the increasing concentration in human mother's milk is driving the alarm and concern. The fetus and neonate are very much more sensitive and vulnerable. There is no NOEL for neurodevelopmental effects established for PBDEs [3]. PBDEs are shown to cause neurodevelopmental deficits in doses on the same molar basis as ortho- and co-planar PCBs [2]. In previous studies we estimated potential costs due to neurodevelopmental effects that exceed $100 billion per year, and dwarf the costs ($120 million a year) of switching to alternatives [4,10]. This hypothetical, or "what-if" scenario is based on PBDEs reaching the 1000 ng/g to 1250 ng/g, and higher levels, in human milk (lipid weight) at various time periods, and having similar effects, as the PCBs studied by the Jacobsons [5], who found these PCB levels to be associated with learning impairments, intellectual deficits, and a 6.2 point loss in IQ scores at the highest exposure.

Conclusions

This analysis suggests that there is a widespread and growing prevalence of hypothyroidism, and the use and cost of medication to treat it, in North America, and that these trends are unexplained. There is also evidence that childhood neurodevelopmental disorders, that can be caused by thyroid disruption, for example, are also widespread and growing, as is the use and cost of prescribed medication, and these are also unexplained. Evidence linking PBDEs to thyroid system disruption exists, as it does for other endocrine disrupting chemicals. The issue is concern about increasing the exposure burden of a human population already expressing significant clinical thyroid and neurodevelopmental disorders, to chemical compounds that have the propensity to be toxic to the thyroid economy and to the neurodevelopmental health of children. It is suggested that urgent research is needed to test the PBDEs for thyroid hormone disruption and developmental neuroxicity (DNT), including the establishment of a NOEL for DNT. Possible cumulative effects of exposure to multiple thyroid disruptive and DNT compounds also should be considered.

References

1. Michael DeVito, Tong Zhou, Michele Taylor, David Ross, and Kevin Crofton. 2001. Organohalogen Compounds, Vol. 53. 1-4.
2. Per Eriksson, Eva Jakobsson, and Anders Fredriksson. 2001. Environmental Health Perspectives, Volume 109, number 9, September 2001. Pp 903-908.
3. Thomas A. McDonald. 2002. Chemosphere 46. Pp 745-755.
4. Tom Muir and Mike Zegarac. 2001. Environmental Health Perspectives, Volume 109, Supplement 6, December. Pp. 885-903.
5. Joseph L. Jacobson and Sandra W. Jacobson. 1996. The New England Journal of Medicine, Volume 335, Number 11, September 12, 1996. Pp. 783-789.
6. Internet search, January, 2003 - www.thyroid.org
7. IMS HEALTH , Canada, Pointe Claire, Quebec. Personal Communication, 2003, and (www.imshealthcanada.com)
8. Internet search, January, 2003 - www.synthroid.com
9. Ryan, John Jake, Benoit Patry, Pat Mills, and Nicole G. Beaudoin. 2002. Organohalogen Compounds, Vol. 58, pp 173-176.
10. Tom Muir, and Mehran Alaee. 2002. Organohalogen Compounds, Vol. 58, pp. 237-240. Also, Poster presentation at Dioxin 2002, Barcelona, Spain. Available on request.