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### Polybrominated Diphenyl Ethers and Cryptorchidism: Confounding or Cause and Effect?

doi:10.1289/ehp.11052

Main et al. (2007) reported that elevated levels of polybrominated diphenyl ethers (PBDEs) in breast milk, but not placenta, were associated with congenital cryptorchidism in Danish and Finnish boys. For the Danish cohort, the researchers used a case-cohort design in which biological samples were collected from all study participants, whereas for the Finnish cohort, they used a nested case-control design. The matching criteria used for Finnish mothers who gave birth to boys with cryptorchidism (measured at birth) and matched Finnish controls included the following: parity, smoking (yes/no), diabetes (yes/no), gestational age ( $\pm 7$  days), and date of birth ( $\pm 14$  days). However, Main et al. (2007) did not provide information on adjustments made to account for the type/severity of diabetes (Virtanen et al. 2006), smoking habits (Kurahashi et al. 2005), alcohol consumption (Damgaard et al. 2007), cesarean section (Hjertkvist et al. 1989; Kurahashi et al. 2005), and other factors that may be associated with cryptorchidism.

Interestingly, Main et al. did note that approximately 12% and 18% of breast milk samples and placentas, respectively, were obtained from diabetic Finnish mothers of cryptorchid boys, compared with 0% of controls (Main et al. 2007), but they conducted no further inquiry on this discrepancy. Damgaard et al. (2007) previously evaluated this same Danish-Finnish cohort and adjusted for confounders and effect modifiers for differences observed based on country, smoking, caffeine intake, alcohol consumption (including binge-drinking episodes), social class, maternal age, parity, maturity, and birth weight. Damgaard et al. (2007) noted an association between maternal alcohol consumption ( $\geq 5$  drinks/week) and transient cryptorchidism. Despite these findings, Main et al. (2007) provided no information on stratified alcohol consumption or other potential confounders, such as caffeine intake or social class.

Main et al. (2007) concluded that an association exists between PBDE levels in breast milk and cryptorchidism in boys, but we should be cautious of this interpretation, given that Main et al. (2007) may not have adequately addressed potential confounders.

M.B. declares he has no competing financial interests. M.L.H. and T.S. work for Albemarle Corporation, a manufacturer of specialty chemicals, including brominated flame retardants.

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Virtanen HE, Tapanainen AE, Kaleva MM, Suomi A-M, Main KM, Skakkebaek NE, et al. 2006. Mild gestational diabetes as a risk factor for congenital cryptorchidism. *J Clin Endocrinol Metab* 91:4862-4865.

### PBDEs and Cryptorchidism: Main et al. Respond

doi:10.1289/ehp.11052R

In their letter, Banasik et al. emphasize that the etiology of cryptorchidism may be multifactorial, and we agree. As stated in the

“Discussion” of our article (Main et al. 2007), exposure to environmental chemicals is only one of many adverse factors that alone, or in combination with each other, may cause testicular maldescent. In turn, lifestyle factors such as smoking and drinking of alcohol may be interrelated, and a certain lifestyle may augment the risk of exposure to endocrine-disrupting chemicals. Genetic factors, complex medical syndromes, and lifestyle factors have been previously identified as risk factors for cryptorchidism, but a significant proportion of cryptorchidism cases still remains unexplained (Virtanen et al. 2007).

In our study (Main et al. 2007) we found an association between the level of polybrominated diphenyl ethers (PBDEs) in breast milk and congenital cryptorchidism. We reported that this remained significant after adjusting for other well-known risk factors for cryptorchidism, such as premature birth or low birth weight for gestational age (Main et al. 2007), as well as adjusting for maternal age, maternal prepregnancy body mass index, parity, and date of childbirth within the cohort, which may affect the level of compounds found in breast milk samples (Main et al. 2007). In the analysis of the entire Danish-Finnish binational cohort, other novel risk factors for cryptorchidism, such as regular maternal alcohol consumption during pregnancy and mild diabetes, were identified (Damgaard et al. 2007; Virtanen et al. 2006).

We originally decided against including additional confounders in our analysis (Main et al. 2007), considering the size of our study group and thus the low number of cases for each confounder, which induces a potential risk of both false-positive and false-negative results (Table 1). However, in a binary logistic regression analysis including all confounders, as suggested by Banasik et al., the association between the level of the seven

**Table 1.** Additional characteristics (number) of the study population who provided breast milk samples.

Characteristic	Denmark		Finland	
	Control (n = 36)	Cryptorchid (n = 29)	Control (n = 32)	Cryptorchid (n = 33)
Delivery type				
Vaginal delivery	28	16	26	23
Vacuum extraction	6	6	2	4
Cesarean section	2	7	4	4
Alcohol consumption (drinks/week)				
0	13	16	26	27
1-4	20	9	6	6
$\geq 5$	3	4	0	0
Alcohol binge-drinking episodes				
Yes	2	2	2	0
No	33	25	28	29
Social class				
High- and low-grade professionals	20	16	17	21
Skilled and unskilled workers	9	7	9	6
Students and unemployed	7	6	6	5

Missing data were treated as missing values in the statistical analysis.

most prevalent PBDEs (BDEs 28, 47, 66, 99, 100, 153, and 154) and congenital cryptorchidism remained significant ( $p < 0.039$ ). Confounders included maternal age, maternal prepregnancy body mass index, gestational age, and weight for gestational age included as continuous variables; parity (1 vs. 2 vs.  $\geq 3$ ), country of origin (Denmark/Finland), social class (high- and low-grade professionals vs. skilled and unskilled workers vs. students and unemployed), smoking (yes/no), diabetes (yes/no), binge episodes (yes/no), and alcohol consumption (0 vs. 1–4 vs.  $\geq 5$  drinks/week) were entered as categorical factors, as described by Damgaard et al. (2007).

In conclusion, the association between perinatal exposure to PBDEs and congenital cryptorchidism was significant even after controlling for confounding factors. Our study could not determine whether a direct causal relationship exists or whether other factors contribute to our findings. Because the exposure to PBDEs is still considerable in some areas, our results should raise concern and stimulate further investigations of human populations.

*The authors declare they have no competing financial interests.*

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## Cryptorchidism: Effects of Maternal Diabetes or PBDEs

doi:10.1289/ehp.11096

It was with great interest that we read the article by Main et al. (2007) regarding polybrominated diphenyl ethers (PBDEs) and cryptorchidism, and we are impressed with the data in humans. Main et al. stated that

the concentration of PBDEs in breast milk was significantly higher in boys with cryptorchidism compared with controls. It is certainly possible that there is a link between fetal PBDE exposure and cryptorchidism; however, we noted that the cohort included children of diabetic mothers. Of the 33 boys with cryptorchidism, 4 in the Finnish group and 1 of 28 in the Danish breast milk–sample group had diabetic mothers. It is widely known that diabetes is a major cause of congenital malformations, and these malformations are dependent on the severity of the diabetes. Therefore, you cannot simply match by diabetes between cases and controls. In a study of 173 mothers with diabetes, we found that 10% of the offspring had congenital malformations related to the severity of the diabetes, classified according to the Priscilla White classification (Koppe et al. 1983). Virtanen et al. (2006), together with Main, published a study reporting an increased risk of cryptorchidism following mild gestational diabetes. In our opinion, the cases of mothers with diabetes should be excluded from analysis of congenital malformations, both in the breast milk group and the placenta group reported by Main et al. (2007).

The group of mothers with diabetes is in itself an interesting group. Are the placenta and breast milk levels of PBDEs or the fat content different between the diabetic cases and the others?

In general, because most PBDEs have phenobarbital-like effects, it seems plausible that they should cause an increase in congenital malformations, such as is seen with phenobarbital (Dessens et al. 1994; Koppe et al. 1973).

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## Cryptorchidism: Main et al. Respond

doi:10.1289/ehp.11096R

ten Tusscher and Koppe point out that maternal diabetes increases the risk of malformations in newborns and suggest that we should have excluded diabetic mothers from the data set. We agree with them that maternal diabetes increases the risk of congenital malformations, although there is only limited evidence for this in the case of cryptorchidism. In our large mother–child cohort from which this data set was derived, we found a significant association between gestational diabetes and congenital cryptorchidism (Virtanen et al. 2006).

We did not initially carry out an analysis corrected for diabetes because the biological samples were not selected with regard to diabetes; therefore data were potentially skewed for this outcome. For the same reason, the total number of mothers with diabetes in each country was low in this data set.

We have now reanalyzed the data, omitting the mothers with diabetes (2 Danish and 4 Finnish mothers for breast milk samples, and 2 Danish and 10 Finnish mothers for placentas). In a binary logistic regression analysis including all relevant confounders (maternal age, maternal prepregnancy body mass index, gestational age, weight for gestational age, parity, and country of origin), the association between the level of the seven most prevalent polybrominated biphenyl ethers (PBDEs) in breast milk (BDEs 28, 47, 66, 99, 100, 153, and 154) and congenital cryptorchidism remained significant ( $p < 0.032$ ), with a median level (2.5th–97.5th percentiles) of 3.16 ng/g fat (1.08–21.73) in controls and 4.19 ng/g fat (1.42–52.64) in cryptorchid boys. The same analysis for the five most prevalent BDEs in placenta (BDEs 47, 153, 99, 100, and 28) remained nonsignificant ( $p = 0.173$ ), with 1.23 ng/g fat (0.56–5.46) in controls and 1.12 ng/g fat (0.37–4.24) in cryptorchid boys.

ten Tusscher and Koppe also suggest the investigation of potential differences between mothers with and without diabetes with respect to fat content in the samples and the concentrations of PBDEs. We previously reported

that the lipid content in breast milk and placenta was higher in Finnish than in Danish samples (Shen et al. 2007). Country of origin was therefore included as a covariate in a binary logistic regression. We found no significant difference between mothers with and without diabetes for fat content in breast milk or placenta ( $p = 0.975$  and  $0.107$ , respectively) or the sum of the most prevalent BDE congeners ( $p = 0.233$  and  $0.317$ , respectively). However, the number of diabetic mothers in our data set is too small to draw any firm conclusions from these results.

In conclusion, the association between perinatal exposure to PBDEs and congenital cryptorchidism was significant after exclusion of diabetic mothers. Exposure to environmental chemicals is, however, one of many adverse factors that alone, or in combination with each other, may cause testicular maldescent (Main et al. 2007). These additional factors include gestational complications, lifestyle, and genetic factors (Virtanen et al. 2007).

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## Tungsten and Cobalt in Fallon, Nevada: Association with Childhood Leukemia

doi:10.1289/ehp.10614

In their article, Sheppard et al. (2007) suggested that the “results in Fallon [Nevada] suggest a temporal correspondence between the onset of excessive childhood leukemia and elevated levels of tungsten and cobalt.” Although the authors reported some interesting findings from their dendrochemistry (tree ring) analysis,

the results, as presented, do not support their conclusion. In fact, if the data they report demonstrate anything, it is that the levels of tungsten in the environment are not causally associated with the cases of leukemia.

Sheppard et al.’s (2007) primary premise is that levels of tungsten increased in Fallon relative to selected comparison towns beginning in the mid-1990s, which the authors contend predates the “1997 onset” of the increased incidence of acute lymphocytic leukemia (ALL) in Churchill County. In fact, when the appropriate comparison is made, the data of Sheppard et al. show that the purported increase in environmental tungsten in Fallon occurred long after the onset of these leukemia cases (i.e., after 2001). Thus, the data they gathered supports the conclusion of the Agency for Toxic Substances and Disease Registry (2003) that the evidence does not support any link between tungsten and these leukemia cases.

Unfortunately, Sheppard et al. (2007) did not provide the actual data in their article, and they did not include error bars or standard deviations for the data points. Regardless of these defects in data presentation, careful interpretation of the graphic representations of the data yields several important insights [the tungsten concentrations listed here are approximate and were obtained from interpolation of the data points from the figures of Sheppard et al. (2007)].

First, tree ring tungsten concentrations in Fallon cottonwoods ranged from 40 to 70 ppm between 1989 and 2000, and then increased to 180 ppm in the 2001–2004 time period. Sweet Home, Oregon, cottonwoods followed a similar pattern, ranging from 50 to 75 ppm between 1989 and 2000 and increasing to 110 ppm for the 2001–2004 period. Thus, no significant increase in tungsten in cottonwood tree rings was observed at either location until the 2001–2004 period, well after the “onset” of the leukemia cases; 12 of the 15 leukemia cases (80%) had been diagnosed by the end of 2000 [Centers for Disease Control and Prevention (CDC) 2003].

Second, it appears that the “comparison town” data comprise the Douglas-fir data from Crawfordsville, Oregon, and data on Douglas-firs and cottonwoods from Sweet Home. Sheppard et al. (2007) acknowledged that “temporal variability of tungsten is higher in the cottonwoods than in the Douglas-firs,” and Douglas-firs exhibit “damped temporal variability.” This is likely to be at least partially due to physiologic differences of tree species (Sheppard et al. 2007). Comparing tungsten levels in responsive cottonwoods in Fallon to groups of trees from comparison towns that included less responsive Douglas-firs is an “apples-to-oranges” comparison, and any differences are more likely related to the

differences in tree species than to different levels of environmental tungsten. This uncertainty is further exacerbated by comparing trees from vastly different environments—the temperate, agricultural areas of northwestern Oregon and the high desert of western Nevada.

Third, Sweet Home cottonwoods exhibited an average of 62 ppm tungsten between 1989 and 2000. Fallon cottonwoods had an average of 60 ppm during this same period. The purported temporal variability between the two locations is nonexistent when like species are compared.

Finally, according to Sheppard et al. (2007), the 1989–1996 period represents two time periods that “predate the 1997 onset of excessive leukemia ...” Yet, compared with those in Fallon, the Sweet Home cottonwoods exhibited slightly higher tungsten concentrations over the 1989–1996 period. Thus, according to the data of Sheppard et al. (2007), environmental tungsten was actually lower in Fallon than in Sweet Home during the period leading up to the diagnosis of the Fallon leukemia cases.

In summary, a critical evaluation of the data leads to a radically different conclusion than that presented by Sheppard et al. (2007). Assuming that the data presented in the article are correct and reflective of environmental conditions in the Fallon area, the data indicate that the purported increase in tungsten levels (if in fact any increase occurred) occurred well after the “onset of the excessive childhood leukemia” and was not unique to this town. This interpretation is consistent with, and further supports, the conclusions that tungsten was not associated with the ALL cluster reached by the CDC in their *Cross-Sectional Exposure Assessment in Fallon* (CDC 2003; Rubin et al. 2007).

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## Tungsten and Cobalt: Sheppard et al. Respond

doi:10.1289/ehp.10614R

First and foremost, our data from Nevada (Sheppard et al. 2007c) should not be quantitatively compared with that from Oregon. We did not make such a comparison in our article; to reinforce separation of these two studies, we described the results in separate subsections and presented data in separate figures. Our Oregon study was an independent test of dendrochemistry for establishing temporal patterns of environmental tungsten in a town with known emission of airborne tungsten. Tungsten emission in Sweet Home, Oregon, began in November 2000, and tree-ring tungsten in cottonwoods near the emission source increased at that time relative to comparison towns in central Oregon. This test demonstrated that dendrochemistry accurately depicts tungsten availability, at least when using cottonwoods. Therefore, dendrochemistry, especially when using cottonwood trees, can be trusted to accurately depict tungsten availability in Fallon, Nevada, where timing of emission of tungsten particles is not known with certainty.

The comparison of real interest was between Fallon and other towns of west-central Nevada. Tree-ring tungsten in Fallon was not significantly different from that of other towns of west central Nevada during the tree-ring period centered on 1991 [Figure 4 in our article (Sheppard et al. 2007c)], before the onset of the leukemia cluster. During the tree-ring period centered on 1995, corresponding to just before the onset of the leukemia cluster, Fallon tree-ring tungsten began trending upward and was significantly higher than Nevada comparison towns. During the following two time periods, overlapping temporally with the childhood leukemia cluster, Fallon tree-ring tungsten continued trending upward and remained higher than Nevada comparison towns, with significance levels at or near  $p = 0.05$  (we provided  $p$ -values in place of error bars), thus indicating the temporal correspondence between elevated tungsten in Fallon and the childhood leukemia cluster.

The Centers for Disease Control and Prevention (CDC) conclusion that tungsten is not mathematically associated with the leukemia cases of Fallon (CDC 2003) is based on case-comparison testing within Fallon. This does not rule out that an underlying association actually exists but is not detectable by the case-comparison technique. Granted, no relation

was reported between leukemia and tungsten exposure, but exposure to tungsten was found to be community-wide, with levels being high both in case children and families and in comparison children and families (CDC 2003). In other words, there was little to no variability in exposure at the community scale (i.e., most everyone in Fallon has been exposed) but high variability in onset of disease (i.e., some people got leukemia but others have not). When variability of an exposure is low relative to individual susceptibility to a disease, genetic studies are needed to identify gene polymorphisms that might make sick children more susceptible to effects of the exposure (Steinberg et al. 2007).

Our environmental research in Fallon has followed an ecologic approach with the philosophy that greater variability in exposure between different towns is more important than the minor variability in exposure within communities (Sheppard et al. 2007a). The entire town of Fallon has been compared environmentally with other towns of west-central Nevada. Multiple environmental indicators have been used, such as outdoor airborne particulates (Sheppard et al. 2006), lichens (Sheppard et al. 2007d), surface dust (Sheppard et al. 2007b), and tree rings (Sheppard et al. 2007c). These indicators incorporate environmental conditions differently from one another, yet they have corroborated one another in showing that airborne tungsten is elevated in Fallon relative to other towns of west-central Nevada or the surrounding desert. Additionally, airborne tungsten particles in Fallon have been identified as anthropogenic in origin, and not natural (Sheppard et al. 2007e).

Even with this preponderance of evidence showing spatial and temporal patterns of airborne tungsten in Fallon, we still have not concluded in any of our reports on Fallon that exposure to tungsten causes leukemia. Quite the opposite: We have acknowledged that environmental data alone cannot lead to such a conclusion and that direct biomedical testing is needed to establish a causal linkage between tungsten and leukemia.

Years ago in an article on disease cluster research, Shimkin (1965) stated that cooperation of industrial management is needed to identify and reduce environmental carcinogens. This comment still rings true today. Kennametal Inc. (Fallon, NV) claims that it supports research in Fallon aimed at understanding the childhood leukemia cluster there (Goodale 2005), but its support is apparently selective. We hereby encourage Kennametal to engage in reasonable dialogue about research in Fallon related to the childhood leukemia cluster.

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## ERRATUM

The April 2008 Focus article [Environ Health Perspect 116:A160–A167 (2008)] includes a misprint. The first paragraph under the subhead “How Much Is Enough?” should read: “Gilchrest points out a problem with the literature: ‘Everyone recommends something different, depending on the studies with which they are most aligned. One study reports an increased risk of prostate cancer for men with 25(OH)D levels above 90 ng/mL, for example [in contrast with the idea that more vitamin D is more protective against cancer].’” *EHP* regrets the error.