Published in final edited form as:

Chemosphere. 2015 January ; 0: 178–186. doi:10.1016/j.chemosphere.2014.08.007.

Maternal exposure to brominated flame retardants and infant Apgar Scores

Metrecia L. Terrell^a, Kathleen P. Hartnett^a, Hyeyeun Lim^b, Julie Wirth^{c,d}, and Michele Marcus^{a,e,f}

^aDepartment of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA

^bDepartments of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas, Houston, TX

^cDepartments of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI

^dDivision of Environmental Health, Bureau of Epidemiology, Michigan Department of Community Health, Lansing, MI

^eDepartment of Pediatrics, Emory University, Atlanta, GA

^fDepartment of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA

Abstract

Brominated flame retardants (BFRs) and other persistent organic pollutants have been associated with adverse health outcomes in humans and may be particularly toxic to the developing fetus. We investigated the association between *in utero* polybrominated biphenyl (PBB) and polychlorinated biphenyl (PCB) exposures and infant Apgar scores in a cohort of Michigan residents exposed to PBB through contaminated food after an industrial accident. PBB and PCB concentrations were measured in serum at the time the women were enrolled in the cohort. PBB concentrations were also estimated at the time of conception for each pregnancy using a validated elimination model. Apgar scores, a universal measure of infant health at birth, measured at 1 and 5 minutes, were taken from birth certificates for 613 offspring born to 330 women. Maternal PCB concentrations at enrollment were not associated with below–median Apgar scores in this cohort. However, maternal PBB exposure was associated with a dose–related increase in the odds of a below–median Apgar score at 1 minute and 5 minutes. Among infants whose mothers had an estimated PBB at conception above the limit of detection of 1 part per billion, the odds ratio was 2.32 (95 % CI: 1.22– 4.40); for those with PBB 2.5 ppb the OR=2.62 (95% CI: 1.38-4.96; test for trend $p < 0.01$). Likewise, the odds of a below–median 5–minute Apgar increased with higher maternal PBB

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Corresponding Author: Metrecia Terrell Emory University 1518 Clifton Rd. Mailstop: 1518-002-3BB Atlanta, GA 30322
404-727-2683 (phone) 404-727-8737 (fax) mterrel@emory.edu.

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The authors have no competing financial interests.

at conception. It remains critical that future studies examine possible relationships between *in utero* exposures to brominated compounds and adverse health outcomes.

Keywords

brominated flame retardants; polybrominated biphenyls; polychlorinated biphenyls; *in utero* exposures; infant Apgar scores

INTRODUCTION

Apgar scores are an important measure of neonatal health at birth. The standardized scores, introduced by Dr. Virginia Apgar (Apgar, 1953), are now used universally. At 1 and 5 minutes after delivery, neonates are scored between 0 and 2 on each of five critical indicators: heart rate, respiratory effort, muscle tone, skin color, and reflex irritability. Points for these five indicators are summed to get the total Apgar score, which ranges from 0 to 10.

The scores are used to assess the newborn's overall condition at birth. Infants with low Apgar scores typically require interventions that can include oxygen, clearing fluid from the airway, or stimulation to achieve a normal heart rate. Apgar scores that remain low at 5 minutes indicate poor response to resuscitation and are associated with neonatal mortality (American Academy of et al., 2006).

Polybrominated biphenyl (PBB) and polychlorinated biphenyl (PCB) have not been manufactured in North America since the 1970s, when most industrialized nations banned production based on evidence of their toxicity. But concerns over their health effects remain, because they are persistent in biological systems, accumulate in adipose tissue, and have long half-lives (Agency for Toxic Substances and Disease Registry (ATSDR), 2000, 2004; Birnbaum and Staskal, 2004). Both chemicals cross the placental barrier and enter the fetal bloodstream (Jacobson et al., 1984; Guvenius et al., 2003). Similar brominated flame retardants, including some mixtures of polybrominated diphenyl ether (PBDE), continue to be produced. Surveys show widespread environmental contamination from PBDEs, with particularly high levels of exposure in the U.S. (Sjodin et al., 2008).

Animal studies have shown that *in utero* PBB exposure is associated with decreased litter size, reduced fetal birth weight, shortened gestational period, and increased risk of spontaneous abortion (Jackson and Halbert, 1974; Corbett et al., 1975; Moorhead et al., 1977; Lambrecht et al., 1978; Welsch and Morgan, 1985). In humans, studies of women who were exposed to PBB when they were children or adults did not show a consistent association between exposure level and gestational age or birth weight of their infants (Humble and Speizer, 1984; Givens et al., 2007; Small et al., 2007). However, a study of *in utero* women who were exposed to PBB suggested that those with higher exposures during this critical window had increased odds of spontaneous abortion when they reached adulthood and became pregnant, compared to those with the lowest exposure (Small et al., 2011).

For PCB, some human studies have found statistically significant associations with spontaneous abortion (Bercovici et al., 1983; Leoni et al., 1989), while others have not (Dar et al., 1992; Axmon et al., 2004). There was a suggested, although not statistically significant, increase in stillbirth among women in the Yucheng cohort, who were exposed to high levels of PCB through contaminated cooking oil (Yu et al., 2000). However, other studies have not found an increase in stillbirths (Dar et al., 1992) or spontaneous abortions (Axmon et al., 2004) among women with higher PCB levels. In a study of prenatal exposure to persistent organic pollutants, Wang and colleagues found that Apgar scores were slightly lower in infants with the highest exposure to dioxin-like polychlorinated biphenyl (PCBs), although the association did not reach statistical significance (Wang et al., 2005). Tan found lower 1-minute Apgar scores associated with the presence of PCB congeners in umbilical cord blood samples (Tan et al., 2009).

A cohort of Michigan residents, many of whom were exposed to unusually high levels of PBB through contaminated food, includes infants potentially exposed to both PBB and PCB *in utero*. In the summer of 1973, a company that produced both PBB, marketed as FireMaster, and a supplement for livestock feed, called NutriMaster, switched the shipments, sending at least 500 pounds of PBB to Michigan farms. Health effects in pregnant cows given contaminated feed included longer gestation, large calves, and increased mortality of both cows and calves. Thousands of Michigan residents were exposed to PBB through the consumption of contaminated meat, eggs, and dairy products before affected farms were quarantined in May 1974 (Jackson and Halbert, 1974; Carter, 1976; Kay, 1977; Halbert and Halbert, 1978; Fries, 1985). Although FireMaster did not contain PCB, these Michigan families were potentially exposed to PCB from other sources, such as contaminated fish in the Great Lakes region and farm silos lined with PCB. Members of the cohort have much higher PBB levels than the U.S. population, but PCB levels similar to those found in other studies of U.S. residents (Kreiss, 1985).

To date, no studies have analyzed Apgar scores after *in utero* exposure to PBB. In this study, we examine whether women's serum concentrations of PBB and PCB at enrollment into the study and PBB estimated at the time of conception are associated with low Apgar scores in their offspring.

MATERIALS AND METHODS

Population

In 1976, the Michigan Department of Community Health (MDCH) began enrolling Michigan residents who lived on quarantined farms or received food from quarantined farms into the Michigan Long-Term PBB Study (~ 4,500 individuals). At enrollment, participants completed detailed questionnaires to capture demographic, health, and lifestyle information. In addition, a blood sample was collected from most participants. The cohort has been followed prospectively since enrollment, with periodic updates of health status and collection of additional blood samples. Two telephone interviews of female participants completed in 1997–1998 and 2003–2006 included questions about reproductive history, health, and lifestyle.

All infants in this study were born at least 4 years after the PBB incident and thus were potentially exposed to PBB for the full *in utero* period. We identified eligible offspring from the 1,930 women who participated in the enrollment interviews. Of these, 1,749 had a serum PBB measurement and 668 had electronic vital record data available in the state of Michigan. Women did not have electronic vital record data for a number of reasons: no pregnancies, no live births, all births prior to 1978, the year when electronic birth records were available in Michigan, or no live births in Michigan. These 668 remaining women had 1,443 live birth offspring in the vital records database. Apgar scores were not available on most birth records until 1989, so we were only able to include 87 births between 1978-88. The remaining 554 birth records were from 1989 to 2005. Every birth record that had a 1 minute Apgar score also had a 5 minute Apgar score. After excluding birth records missing Apgar scores (n=2 between 1989 and 2005), or with multiple births (n= 26), we were left with 613 offspring from 330 women.

The protocols for this study have been approved by the Institutional Review Board at Emory University in Atlanta, GA and the Michigan Department of Community Health. All women gave informed consent and consent to release birth certificate information for their offspring.

Exposure Assessment

The residents of Michigan were exposed to a mixture of PBB, mostly PBB-153 or 2,2',4,4',5,5'-hexabromobiphenyl (approximately 60% of total PBB) (Agency for Toxic Substances and Disease Registry (ATSDR), 2004). Maternal serum samples collected at enrollment (1976-1978) and at other times were analyzed for PBB-153 by the Michigan Department of Community Health Bureau of Laboratories. Serum concentrations of PBB were measured using gas chromatography with electron capture detection (Burse et al., 1980; Needham et al., 1981). The limit of detection (LOD) was 1 part per billion (ppb). The coefficients of variation for PBB quantification ranged from 7% to 14% (Needham et al., 1981). Serum PCB concentrations were based on Aroclor 1254, with a LOD of 5.0 ppb. The coefficients of variation for PCB ranged from 12% to 30% (Needham et al., 1981). The Bureau of Laboratories used a double determination method, which measured both total PBB and total PCB exposure in the same serum sample. Samples were collected from non-fasting individuals, and serum lipids were not measured.

We used maternal enrollment PBB concentrations in this study, but also estimated serum PBB at the time of the offspring's conception. We calculated an estimate (λ) from the one-compartment first-order mixed effects elimination model (Terrell et al., 2008), using these parameters: the mother's body mass index at enrollment, her smoking history, and her pregnancy and breastfeeding histories. We then used the following formula: [estimated PBB = enrollment PBB $\times$ exp (λt)], where (t) is the time between the offspring's conception date and the date when the mother's enrollment serum sample was collected. Because PBB body burden declines over time, we expect the estimated PBB concentration at conception to better indicate the offspring's *in utero* exposure than PBB concentration measured at enrollment.

Assessment of Apgar scores and risk factors

Electronic birth records of offspring were used to obtain Apgar scores at 1 and 5 minutes, as well as known risk factors for low scores, including the infant's birth weight, gestational age, and method of delivery, maternal smoking and alcohol consumption during pregnancy, maternal education and payment source for hospital bill (proxies for socioeconomic status), maternal parity, complications of labor and delivery (includes presence of meconium, fetal distress, breech position), maternal hypertension during pregnancy (includes pregnancy-related hypertension and eclampsia) and maternal history of diabetes (chronic or gestational) (Catlin et al., 1986; Jonas et al., 1990; Hegyi et al., 1998; Thorngren-Jerneck and Herbst, 2001). We also considered maternal age as a risk factor, due to its association with infant birth weight and neonatal mortality (Naeye, 1983; Geronimus, 1986). In addition, we considered trimester when prenatal care began, weight gain during pregnancy, sex of the infant, abnormal conditions of the infant (includes assisted ventilation and meconium aspirate syndrome), and congenital anomalies of the infant as risk factors for low Apgar scores. We used information from the telephone interviews on hypertension (includes pregnancy related hypertension, pre-eclampsia and toxemia), diabetes, and alcohol consumption when it was missing from the electronic birth records. Parity and gravidity were captured from the telephone interviews or from the electronic birth records if the mother did not participate in the interviews.

Statistical Analyses

Risk factors for low Apgar scores were categorized as follows: infant's birth weight (<2,500 grams, 2,500-3,499 grams, 3,500-3,900 grams, or ≥4,000 grams), infant's gestational age (<37 weeks, 37-41 weeks, or ≥42 weeks) both in accordance with clinical definitions for low birth weight and high birth weight or pre-term and post-term, respectively; maternal age (<25, 25-29, 30-34 or ≥35 years); maternal education (HS or >HS); payment source for the hospital bill (private insurance or other); maternal prenatal care (care initiated within the first trimester yes or no); maternal weight gain during pregnancy (<30 lbs, 30-39 lbs, or ≥40 lbs); method of delivery (unassisted vaginal, assisted vaginal or Cesarean section), maternal parity (0, 1 or ≥2 prior live births); and maternal gravidity (0, 1, 2 or ≥3 prior pregnancies). Maternal alcohol consumption, smoking status, complications of labor and delivery, hypertension during pregnancy, history of diabetes, and abnormal conditions or congenital anomalies of the infant were dichotomized as no or yes.

In order to determine which variables we should include in the model as potential confounders, we used a Directed Acyclic Graph (DAG). For the association between enrollment PBB and Apgar score, we identified maternal smoking, breastfeeding, and BMI prior to enrollment as potential confounders. Because most of the women in our study were children at the time of PBB exposure (median age=8), only 14 women had been pregnant and 16 reported smoking between the time of the PBB contamination and enrollment. For the analysis modeling the association between PBB concentration at enrollment and infant Apgar score, we excluded the small number of women who smoked or were pregnant before enrollment and controlled for maternal BMI at the time of enrollment in the study. None of these covariates were potential confounders in our model using estimated PBB at the time of conception, because the elimination model that we used to estimate conception PBB

includes maternal parity and breastfeeding history, smoking history, and enrollment BMI, which implicitly controls for these variables. For the model of the association between maternal PCB levels and infant Apgar score, we included maternal smoking, parity, education and age at delivery as potential confounders.

Because the exposure concentrations for PBB and PCB were skewed, we used cut-points at or below the LOD, up to the median, and at or above the median for enrollment PBB (median=4 ppb) and estimated PBB at conception (median=2.5 ppb). Over half of the infants were born to mothers with undetectable PCB concentrations. Thus, we dichotomized enrollment PCB at the LOD (< 5 ppb or ≥ 5 ppb).

We modeled the odds of low Apgar scores in relation to PBB and PCB exposure using generalized estimating equations (GEE). Separate models were fit for enrollment PBB, PCB, and estimated PBB at conception. First, we used ordinal logistic regression and a cumulative logit model for the odds of lower-ordered Apgar scores. This ordinal model required an independent correlation structure so did not allow us to adjust the variance to account for children born to the same mother. Apgar scores at 1 minute (5, 6, 7, 8, 9–10 points) and 5 minutes (7, 8, 9, 10 points) were categorized because of sparse numbers. Then, we used dichotomous logistic regression to model the odds of Apgar scores below the median (8 for 1 minute and 9 for 5 minutes). In the dichotomous model, we used an exchangeable correlation structure to account for the lack of independence between pregnancies from the same mother.

In addition, we considered models that assessed the interaction between enrollment PBB and PCB. We also performed tests of trend for the exposures, treating each exposure as an ordinal variable. Finally, we repeated the separate models for PBB and PCB in a reduced sample that excluded infants with abnormal conditions, congenital anomalies, of low birth weight or small for gestational age, infants born to mothers with complications of labor and delivery, or assisted vaginal deliveries. All analyses were performed using SAS software, Version 9.3 (SAS Institute Inc. Cary, NC).

RESULTS

The mothers of the offspring in this study (n= 330) were on average 8 years old at the time of the accident in 1973 (range: infancy-28 years). Enrollment PBB concentrations ranged from not detectable (12%) to 1490 ppb (25P=1 ppb; 75P=6 ppb; 90P=17 ppb) and enrollment PCB concentrations ranged from not detectable (55%) to 78 ppb (25P=not detectable; 75P=6 ppb; 90P=9 ppb). Maternal PBB and PCB concentrations were not highly correlated (Spearman $r=0.10$, $p=0.02$).

The distribution of Apgar scores at 1 and 5 minutes by estimated PBB concentrations at conception for the 613 infants is displayed in Figure 1. Slightly more infants with higher estimated PBB concentrations had lower 1-minute Apgar scores (at 7 points and 8 points). For 5-minute Apgar scores, few infants had scores < 7 points (2.3%), and of these, none were in the lowest estimated PBB concentration group (PBB < 1 ppb). Additionally, slightly more infants with estimated PBB concentrations < 1 ppb had Apgar scores of 9–10 points.

The demographic characteristics of mothers and infants and unadjusted odds ratios for having lower Apgar scores (defined as below the median, <8 for 1 minute, and <9 for 5 minutes) are given in Table 1. Low birth weight was significantly associated with increased odds of having low Apgar scores at both 1 and 5 minutes (1 minute, OR= 4.76, 95% CI: 1.77-12.82; 5 minutes, OR= 5.92, 95% CI: 2.07-16.89). Similarly, this was true for pre-term infants (1 minute, OR= 2.50, 95% CI: 1.00-6.21; 5 minutes, OR= 4.23, 95% CI: 1.61-11.15). The other factors associated with increased odds of having lower Apgar scores at 1 and 5 minutes were infants with abnormal conditions at birth and infants born to mothers who experienced complications of labor and delivery. Infants who were their mother's first live birth were also more likely to have a low Apgar score at 1 and 5 minutes.

When we modeled Apgar scores with ordinal logistic regression (Table 2), we found a significant odds of having lower ordered 1-minute Apgar scores for higher levels of estimated PBB concentrations at conception (n=523 infants, >1-<2.5 ppb, OR=1.69, 95 % CI: 1.14-2.51; 2.5 ppb, OR= 1.81, 95% CI: 1.21-2.71). For maternal enrollment PBB concentrations 4 ppb, there was a significant odds ratio for having lower ordered Apgar scores (OR=1.61, 95% CI: 1.05-2.47). The odds ratios for maternal enrollment PBB concentrations (>1 -<4 ppb) and 1-minute Apgar scores and the estimated or maternal enrollment PBB concentrations and 5-minute Apgar scores did not reach statistical significance.

When we removed the infants who were low birth weight or small for gestational age, had congenital anomalies or abnormal conditions at birth, or were born to mothers who had complications of labor and delivery or assisted vaginal deliveries, (Table 2, with infants excluded), there remained a significant odds of lower 1-minute Apgar scores for estimated PBB concentrations at conception 2.5 ppb (n= 339 infants, OR= 1.85, 95% CI: 1.10-3.12). The other results among these infants were of lower magnitude with insignificant confidence intervals.

When we used dichotomous logistic regression (Table 3) modeling the odds of low Apgar scores (below the median) and adjusting for infants born to the same mother, the odds ratios were of higher magnitude but with wider confidence intervals than those in Table 2. There was at least a 2-fold increase in the odds of having low Apgar scores for infants with an estimated PBB concentrations at conception above 1 ppb (n= 523 infants, >1-<2.5 ppb, OR= 2.32, 95 % CI: 1.22-4.40; 2.5 ppb, OR= 2.62, 95% CI: 1.38-4.96; test for trend $p < 0.01$). For Apgar scores at 5 minutes, infants with estimated PBB at conception above 1 ppb had a similar 2-fold increase in the odds of low Apgar scores (n= 523 infants, >1-<2.5 ppb, OR= 2.58, 95 % CI: 1.15-5.79; 2.5 ppb, OR= 2.40, 95% CI: 1.08-5.35; test for trend $p = 0.04$). Confidence intervals for this outcome, however, were wider than for Apgar scores at 1 minute. The odds ratios for infants with maternal enrollment PBB concentrations above 1 ppb showed the same trend for 1-minute and 5-minute Apgar scores, with attenuated odds ratios and insignificant confidence intervals (n=555 infants).

When we removed the infants who were low birth weight or small for gestational age, had abnormal conditions or congenital anomalies at birth, or were born to mothers who had complications of labor and delivery or assisted vaginal deliveries (Table 3, with infants

excluded), the dichotomous logistic regression odds ratios showed the same trends, but were of lower magnitude with insignificant confidence intervals. We did not find a significant association between PCB concentrations ≥ 5 ppb and odds of having a low Apgar score at 1 or 5 minutes using ordinal logistic regression or dichotomous logistic regression. In the models that contained both enrollment PBB and PCB, the odds ratios were similar to Tables 2 and 3. Finally, the interaction term of enrollment PBB and PCB exposures was not significant (1 minute Apgar scores, $p=0.21$; 5 minute Apgar scores, $p=0.16$).

To assess whether age at exposure to PBB affected our results, we modeled the odds of low Apgar scores (below the median) stratified by age at exposure (<9 years and ≥ 9 years), adjusting for infants born to the same mother (Table 4). We found a 3-fold increase in the odds of having low 1-minute Apgar scores for estimated PBB concentrations at conception above 1 ppb only in women who were exposed to PBB when they were younger than 9 years old ($n=297$ infants, $>1-2.5$ ppb, OR= 3.03, 95 % CI: 1.29-7.08; ≥ 2.5 ppb, OR= 3.54, 95% CI: 1.48-8.47). The odds ratios were higher for estimated PBB concentrations at conception and 5-minute Apgar scores, but had wider confidence intervals. The models with enrollment PBB concentrations had attenuated odds ratios. We did not find an effect of PBB exposure on Apgar scores in infants born to women who were exposed to PBB when they were 9 years or older.

DISCUSSION

We found an association between *in utero* PBB exposure and increased odds of Apgar score below the median at 1 and 5 minutes after birth. This appears to be a novel finding – we are unaware of any other studies in the literature that examined the effect of PBB on Apgar score.

It is not surprising that we found an association between Apgar scores and PBB level at conception but not at enrollment. The women's primary exposure to PBB ended 1974, when the contamination was discovered and the affected animals were destroyed. Most women's body burdens of PBB then slowly declined over time. Because a variety of factors, including smoking and breastfeeding, affect the elimination rate of PBB, our model of exposure at the time of conception is a better measure of exposure than initial PBB levels measured years earlier. Many of the women in our study were children or teenagers when they were exposed to PBB, with a median time from a woman's exposure to her infant's birth of 20.4 years (range 4.8-32.4 years, interquartile range 7.9 years).

It is interesting that we found an association between PBB level and infant Apgar score in women who were exposed to PBB before age 9, but not after. PBB may be most harmful during critical windows of development, such as before puberty. Previous studies in this cohort also found an interaction between PBB dose and age at exposure in a study of the risk of spontaneous abortion. Women who were themselves exposed to high levels of PBB *in utero* had higher odds of having a spontaneous abortion decades later, when they became pregnant (Small et al., 2011). In contrast, mothers who were exposed to PBB as children or adults did not appear to have an elevated risk of spontaneous abortion (Small et al., 2007).

In our study, low Apgar scores at 1 minute were also associated with infant birth weight <2,500 grams, gestational age of under 37 weeks, abnormal condition of infant, complications of labor and delivery, and the first-born live birth. All of these associations are consistent with the literature (Rogers and Graves, 1993; Thorngren-Jerneck and Herbst, 2001). We found these same risk factors, as well as nulliparity, associated with low Apgar scores at 5 minutes.

Other risk factors for a low Apgar score reported in the literature include breech position, fetal distress, umbilical cord complications, congenital abnormalities (Jonas et al., 1990), pre-eclampsia, and anemia at delivery (Rogers and Graves, 1993). When we excluded infants who were of low birth weight or small for gestational age, had congenital anomalies or abnormal conditions at birth, or were born to mothers who had complications of labor and delivery or assisted vaginal deliveries, we did not see as strong of an association between PBB level and Apgar scores. It is thus possible that the harmful effect of PBB on neonatal health is indirect, with exposure increasing the likelihood of developing one or more of these risk factors.

We did not find a clear trend of higher maternal blood pressure with increasing PBB concentrations and had insufficient evidence to examine whether PBB increases the risk of pre-eclampsia. As in a previous paper from this cohort, (Givens et al., 2007), we did not find a consistent relationship between PBB level and gestational age or birth weight.

Thus, the mechanism by which maternal PBB could affect neonatal health requires further investigation. Interestingly, we did find that moderate PBB exposure was associated with a higher number of infants classified on the birth certificate as having abnormal conditions at birth, which included meconium aspirate syndrome, assisted ventilation and other conditions. One mechanism by which brominated flame retardants could cause neonatal respiratory distress is by disrupting the hormones that regulate fetal lung maturation. Evidence from animal studies suggests that estrogens could be important to lung development (Patrone et al., 2003; Gortner et al., 2013).

Our results did not show an association between PCB exposure and infant Apgar scores in this population. One possible reason that we did not replicate the association found by Tan and colleagues (Tan et al., 2009) may be the lower levels of PCB exposure among this group of women in Michigan. Fewer than half of the women in our study had detectable levels of PCB at enrollment, possibly because many were children when they enrolled in the study and had their PCB levels tested (74% were 16 years old). These children of Michigan farm families may not have consumed as much fish. Women who participated in Tan's study in Singapore, by contrast, reported eating fish more often (mean of 183 g per week) than poultry or beef, and the women's fish consumption was positively correlated with levels of PCB in adipose tissue. Tan and colleagues did not investigate other contaminants in seafood, such as inorganic lead and mercury, but suggested that these chemicals might also have contributed to the lower Apgar scores in exposed infants.

Although the women's PCB levels are comparable to other studies of U.S. populations from the same time period (Kreiss, 1985), our limits of detection for both PCB and PBB at

enrollment were high relative to today's standards. Our referent group thus includes women who had some exposure to both chemicals, and our ORs estimate the effect of high exposure compared to low, rather than exposed to unexposed. These higher LODs make it difficult to extrapolate our findings to populations with lower levels of exposure.

One limitation of our PCB analysis is that we had to use enrollment levels as our exposure. We did not have repeated PCB measurements over time, so could not construct an elimination model to estimate the mother's PCB levels at the time of conception, as we did for PBB. Although the primary exposure to PBB occurred during the contamination incident of 1973-74, study participants' exposure to PCBs likely continued over time. The U.S. banned the manufacture of PCBs in 1977, but these chemicals remain in sediment, have long half-lives, and accumulate up the food chain. Thus many fish caught in Michigan and other parts of the world still contain PCBs, and remain a source of potential exposure decades after the ban (Hopf et al., 2009; Xue et al., 2014). For women who ate significant quantities of fish after they enrolled in the cohort, serum PCB at enrollment would underestimate the *in utero* exposure of their infants born years later. Compared to a typical population, the infants in our study have high levels of exposure to brominated flame retardants. Most of the infants in our study were born more than a decade after the contamination in 1973-4, by which time the mothers' levels had declined, but were still well above background population levels of brominated compounds (Sjodin et al., 2008). If there is a dose-dependent relationship between PBB exposure and depressed Apgar scores, our observed ORs in this sample of births would be closer to the null than in a sample with more births at the highest level of exposure in 1974, but stronger than might be seen in a population with background levels of PBB exposure.

The use of Apgar score as an outcome has certain limitations. Studies have reported variability among health care workers in assigning Apgar scores (O'Donnell et al., 2006; Rudiger et al., 2009). Despite this variability, it has been shown in large scale studies that Apgar scores are closely associated with infant mortality (Casey et al., 2001; Thorngren-Jerneck and Herbst, 2001).

In our population, Apgar scores were highly skewed, and few infants had Apgar scores below 7 at either 1 or 5 minutes. We considered two different classifications of Apgar scores, each with a strength and limitation. The ordinal model allowed us to look at Apgar score in finer detail but could not adjust for the lack of independence in births to the same mother. The dichotomous model did account for the correlation between siblings but grouped together all Apgar scores below the median (a score of 8 for 1 minute and 9 for 5 minutes). These broad groupings in the dichotomous model, while yielding similar results, may have obscured the association between PBB exposure and Apgar scores that we saw more clearly in the ordinal model. We had inadequate power to investigate whether PBB exposure is associated with Apgar scores below 7 points. However, the data, while limited, do suggest increased odds of lower Apgar scores in infants born to mothers with higher serum PBB concentrations at conception and enrollment.

Given these findings, we recommend additional studies in this cohort and others. Although PBBs are no longer manufactured, exposure to similar brominated flame retardants remains

ubiquitous. It is thus critical that future studies examine a possible relationship between *in utero* exposures to brominated compounds and adverse health outcomes.

Acknowledgments

Funding was provided by the National Institutes of Health (R01 ES08341, R01 ES12014), the U.S. Environmental Protection Agency (R 825300), and the Centers for Disease Control and Prevention (U37/CCU500392). We thank the staff of the Michigan Department of Community Health, participants of the Michigan Long-Term PBB study and Glenn Copeland, State Registrar and Director, Michigan Division for Vital Records and Health Statistics, for providing the linked electronic birth record data used in this study.

ABBREVIATIONS

BFR	brominated flame retardant
PBB	polybrominated biphenyl
PCB	polychlorinated biphenyl
MDCH	Michigan Department of Community Health
PPB	parts per billion
PBDEs	polybrominated diphenyl ethers
OR	odds ratio
CI	confidence interval
LOD	limit of detection

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HIGHLIGHTS

- A cohort of Michigan residents were exposed to high levels of PBB after an industrial accident.
- We investigated the association between *in utero* exposure to PBB and PCB and infant Apgar scores.
- Infants whose mothers had detectable PBB were more likely to have below-median Apgar scores.
- *In utero* PCB exposure was not associated with Apgar scores in this cohort.

Figure 1.
Distribution of one-minute and five-minute Apgar scores by estimated PBB concentrations at conception (n=613)

Table 1

Characteristics of Mothers and Infants According to Apgar Scores (n=613)

Characteristic	N	%	Apgar Scores at 1 minute				Apgar Scores at 5 minutes			
			1-7 N (%)	8-10 N (%)	Unadjusted OR	95% CI	1-8 N (%)	9-10 N (%)	Unadjusted OR	95% CI
Infant birth weight										
< 2,500 grams	23	3.8	10 (9.0)	13 (2.6)	4.76	(1.77 - 12.82)	8 (13.1)	15 (2.7)	5.92	(2.07 - 16.89)
2,500-3,499 grams	267	43.5	53 (47.8)	214 (42.6)	1.55	(0.94 - 2.57)	27 (44.3)	240 (43.5)	1.23	(0.66 - 2.28)
3,500-3,999 grams	227	37.0	31 (27.9)	196 (39.0)	-	-	19 (31.1)	208 (37.7)	-	-
4,000 grams	96	15.7	17 (15.3)	79 (15.8)	1.35	(0.69 - 2.63)	7 (11.5)	89 (16.1)	0.87	(0.37 - 2.07)
Infant gestation										
<37 weeks	23	3.8	8 (7.2)	15 (3.0)	2.50	(1.00 - 6.21)	7 (11.5)	16 (2.9)	4.23	(1.61 - 11.15)
37-41 weeks	534	87.1	96 (86.5)	438 (87.2)	-	-	50 (81.9)	484 (87.7)	-	-
42 weeks	56	9.1	7 (6.3)	49 (9.8)	0.65	(0.27 - 1.55)	4 (6.6)	52 (9.4)	0.74	(0.25 - 2.16)
Infant gender										
Male	339	55.3	65 (58.6)	274 (54.6)	-	-	34 (55.7)	305 (55.3)	-	-
Female	274	44.7	46 (41.4)	228 (45.4)	0.85	(0.54 - 1.34)	27 (44.3)	247 (44.7)	0.98	(0.58 - 1.67)
Abnormal conditions of infant										
No	502	89.3	80 (80.8)	422 (91.4)	-	-	41 (75.9)	461 (90.8)	-	-
Yes	60	10.7	19 (19.1)	41 (8.9)	2.49	(1.35 - 4.60)	13 (24.1)	47 (9.2)	3.12	(1.52 - 6.37)
Congenital Anomalies of infant										
No	517	98.7	88 (98.9)	429 (98.6)	-	-	46 (97.9)	471 (98.7)	-	-
Yes	7	1.3	1 (1.1)	6 (1.4)	0.76	(0.09 - 6.36)	1 (2.1)	6 (1.3)	1.60	(0.19 - 13.62)
Age of mother at infant's birth										
<25 years	138	22.5	36 (32.4)	102 (20.3)	1.97	(1.13 - 3.43)	19 (31.2)	119 (21.5)	1.61	(0.83 - 3.11)
25-29 years	210	34.3	32 (28.8)	178 (35.5)	-	-	19 (31.2)	191 (34.6)	-	-
30-34 years	201	32.8	35 (31.5)	166 (33.1)	1.19	(0.69 - 2.04)	19 (31.2)	182 (33.0)	1.04	(0.54 - 2.03)
35 years	64	10.4	8 (7.2)	56 (11.2)	0.81	(0.35 - 1.83)	4 (6.4)	60 (10.9)	0.67	(0.22 - 2.02)
Maternal education										
H.S.	223	36.8	42 (38.5)	181 (36.4)	1.10	(0.69 - 1.75)	16 (26.7)	207 (37.9)	0.60	(0.32 - 1.11)
>H.S.	383	63.2	67 (61.5)	316 (63.6)	-	-	44 (73.3)	339 (62.1)	-	-
Payment for hospital bill										

Characteristic	N	%	Apgar Scores at 1 minute				Apgar Scores at 5 minutes			
			1-7 N (%)	8-10 N (%)	Unadjusted OR	95% CI	1-8 N (%)	9-10 N (%)	Unadjusted OR	95% CI
private insurance	453	86.1	78 (86.7)	375 (86.1)	-	-	45 (95.7)	408 (85.2)	-	-
Other	73	13.8	12 (13.3)	61 (13.9)	0.94	(0.48 - 1.86)	2 (4.3)	71 (14.8)	0.25	(0.06 - 1.05)
Maternal prenatal care ^a										
1st trimester	520	86.5	92 (86.8)	428 (86.5)	-	-	52 (91.2)	468 (86.0)	-	-
> 1st trimester	81	13.5	14 (13.2)	67 (13.5)	0.98	(0.53 - 1.81)	5 (8.8)	76 (14.0)	0.59	(0.22 - 1.55)
Maternal weight gain during pregnancy										
<30 lbs	239	48.2	44 (52.4)	195 (47.4)	-	-	21 (50.0)	218 (48.0)	-	-
30-39 lbs	167	33.7	30 (35.7)	137 (33.2)	0.98	(0.58 - 1.66)	14 (33.3)	153 (33.7)	0.96	(0.48 - 1.94)
40 lbs	90	18.1	10 (11.9)	80 (19.4)	0.55	(0.27 - 1.15)	7 (16.7)	83 (18.3)	0.89	(0.37 - 2.14)
Method of delivery										
Unassisted vaginal	380	71.8	66 (72.5)	314 (71.7)	-	-	29 (61.7)	351 (72.9)	-	-
Assisted vaginal	24	4.5	6 (6.6)	18 (4.1)	1.57	(0.61 - 4.04)	3 (6.4)	21 (4.3)	1.74	(0.48 - 6.33)
Cesarean section	125	23.6	19 (20.9)	106 (24.2)	0.86	(0.48 - 1.56)	15 (31.9)	110 (22.8)	1.63	(0.81 - 3.30)
Maternal alcohol ingestion ^b										
No	538	90.1	91 (86.7)	447 (91.4)	-	-	52 (91.2)	486 (90.5)	-	-
Yes	56	9.4	14 (13.3)	42 (8.6)	1.71	(0.87 - 3.38)	5 (8.8)	51 (9.5)	0.90	(0.33 - 2.44)
Maternal smoking status ^c										
No	472	89.9	84 (92.3)	388 (89.4)	-	-	42 (89.4)	430 (90.0)	-	-
Yes	53	10.1	7 (7.7)	46 (10.6)	0.71	(0.30 - 1.71)	5 (10.6)	48 (10.0)	1.08	(0.40 - 2.93)
Maternal complications of labor and delivery										
No	390	68.8	57 (56.4)	333 (71.5)	-	-	29 (53.7)	361 (70.4)	-	-
Yes	177	31.2	44 (43.6)	133 (28.5)	1.92	(1.23 - 2.97)	25 (46.3)	152 (29.6)	2.04	(1.17 - 3.56)
Maternal hypertension during pregnancy										
No	523	91.3	97 (95.1)	426 (90.5)	-	-	50 (90.9)	473 (91.3)	-	-
Yes	50	8.7	5 (4.9)	45 (9.5)	0.49	(0.19 - 1.23)	5 (9.1)	45 (8.7)	1.01	(0.38 - 2.71)
Maternal history of diabetes										
No	528	92.8	95 (93.1)	433 (92.7)	-	-	52 (96.3)	476 (92.4)	-	-
Yes	41	7.2	7 (6.9)	34 (7.3)	0.93	(0.39 - 2.26)	2 (3.7)	39 (7.6)	0.44	(0.10 - 1.88)
Maternal parity ^d										

Characteristic	N	%	Apgar Scores at 1 minute				Apgar Scores at 5 minutes			
			1-7 N (%)	8-10 N (%)	Unadjusted OR	95% CI	1-8 N (%)	9-10 N (%)	Unadjusted OR	95% CI
0	206	33.6	50 (45.1)	156 (31.1)	1.76	(1.09 - 2.83)	30 (49.2)	176 (31.9)	1.81	(0.99 - 3.30)
1	209	34.1	32 (28.8)	177 (35.2)	-	-	18 (29.5)	191 (34.6)	-	-
2+	198	32.3	29 (26.1)	169 (33.7)	0.93	(0.53 - 1.64)	13 (21.3)	185 (33.5)	0.75	(0.35 - 1.59)
Maternal gravity ^e										
0	168	27.4	38 (34.2)	130 (25.9)	1.55	(0.94 - 2.58)	24 (39.3)	144 (26.1)	1.55	(0.82 - 2.91)
1	185	30.2	29 (26.1)	156 (31.1)	-	-	18 (29.5)	167 (30.2)	-	-
2	128	20.9	24 (21.6)	104 (20.7)	1.22	(0.68 - 2.18)	11 (18.1)	117 (21.2)	0.87	(0.39 - 1.95)
3+	132	21.5	20 (18.0)	112 (22.3)	0.94	(0.49 - 1.80)	8 (13.1)	124 (22.5)	0.60	(0.25 - 1.45)

Models are adjusted for infants born to the same mother

^aMonth prenatal care began

^bMaternal alcohol ingestion during pregnancy

^cMaternal tobacco use during pregnancy

^dNumber of prior live births

^eTotal number of prior pregnancies

Table 2

Adjusted odds ratios and 95% CIs for having lower order Apgar Scores^a

Models	Apgar Scores at 1 minute					
	All infants			With infants excluded ^b		
	N	OR	95% C.I.	N	OR	95% C.I.
Estimated PBB ^c (ppb)						
1	143	1.00	-	91	1.00	-
>1 - <2.5	187	1.69	(1.14 – 2.51)	120	1.27	(0.76 – 2.12)
2.5	193	1.81	(1.21 – 2.71)	128	1.85	(1.10 – 3.12)
Enrollment PBB ^d (ppb)						
1	127	1.00	-	82	1.00	-
>1 - <4	199	1.31	(0.85 – 2.03)	129	0.80	(0.45 – 1.42)
4	229	1.61	(1.05 – 2.47)	151	1.45	(0.85 – 2.49)
Enrollment PCB ^e (ppb)						
< 5	242	1.00	-	151	1.00	-
5	201	0.91	(0.61 – 1.34)	141	1.09	(0.69 – 1.71)

Models	Apgar Scores at 5 minutes					
	All infants			With infants excluded ^b		
	N	OR	95% C.I.	N	OR	95% C.I.
Estimated PBB ^c (ppb)						
1	143	1.00	-	91	1.00	-
>1 - <2.5	187	1.32	(0.80 – 2.17)	120	0.88	(0.48 – 1.64)
2.5	193	1.38	(0.86 – 2.21)	128	1.25	(0.70 – 2.24)
Enrollment PBB ^d (ppb)						
1	127	1.00	-	82	1.00	-
>1 - <4	199	1.31	(0.77 – 2.23)	129	0.84	(0.44 – 1.62)
4	229	1.29	(0.78 – 2.13)	151	1.22	(0.66 – 2.24)
Enrollment PCB ^e (ppb)						

< 5	242	1.00	-	151	1.00	-
5	201	0.96	(0.57 – 1.59)	141	1.19	(0.64 – 2.23)

^a Apgar scores defined as ordinal variables for 1 minute (5, 6, 7, 8, 9–10) and 5 minutes (7, 8, 9, 10); models not adjusted for infants born to the same mother

^b Models exclude infants with birth weight <2,500 g, gestational age<37 wks, abnormal conditions, congenital anomalies, born to mothers with complications of labor and delivery, or assisted vaginal deliveries

^c Estimated PBB is at the time of conception and calculated from an elimination model that adjusts for the mother's body mass index at enrollment, smoking history, and pregnancy and breastfeeding histories.

^d Enrollment PBB models adjust for the mother's body mass index at enrollment and excludes infants born to mothers who either reported being a smoker at enrollment or being pregnant since 1973.

^e Enrollment PCB models adjust for maternal smoking status, parity, education, and age at delivery

Table 3

Adjusted odds ratios and 95% CIs for Apgar Scores below the median^a

Apgar Scores at 1 minute								
Models	All infants			With infants excluded ^b				
	N	OR	95% C.I.	Trend p-value	N	OR	95% C.I.	T trend p-value
Estimated PBB ^c (ppb)				<0.01				0.10
1	143	1.00	-		91	1.00	-	
>1 - <2.5	187	2.32	(1.22 - 4.40)		120	1.27	(0.54 - 2.97)	
2.5	193	2.62	(1.38 - 4.96)		128	1.93	(0.86 - 4.33)	
Enrollment PBB ^d (ppb)				0.05				0.32
1	127	1.00	-		82	1.00	-	
>1 - <4	199	1.43	(0.77 - 2.65)		129	0.64	(0.27 - 1.52)	
4	229	1.80	(0.99 - 3.26)		151	1.47	(0.69 - 3.14)	
Enrollment PCB ^e (ppb)				-				-
<5	242	1.00	-		151	1.00	-	
5	201	0.98	(0.58 - 1.66)		141	0.99	(0.49 - 2.03)	

Apgar Scores at 5 minutes								
Models	All infants			With infants excluded ^b				
	N	OR	95% C.I.	Trend p-value	N	OR	95% C.I.	T trend p-value
Estimated PBB ^c (ppb)				0.04				0.11
1	143	1.00	-		91	1.00	-	
>1 - <2.5	187	2.58	(1.15 - 5.79)		120	1.39	(0.47 - 4.10)	
2.5	193	2.40	(1.08 - 5.35)		128	2.23	(0.81 - 6.13)	
Enrollment PBB ^d (ppb)				0.16				0.29
1	127	1.00	-		82	1.00	-	
>1 - <4	199	1.67	(0.75 - 3.73)		129	0.80	(0.26 - 2.43)	
4	229	1.81	(0.83 - 3.96)		151	1.68	(0.64 - 4.42)	
Enrollment PCB ^e (ppb)				-				-
<5	242	1.00	-		151	1.00	-	

5	201	0.59	(0.29 - 1.26)	141	0.65	(0.22 - 1.92)
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- ^a Apgar scores below the median are <8 for 1 minute and <9 for 5 minutes; all models adjusted for infants born to the same mother
- ^b Models exclude infants with birth weight <2,500 g, gestational age<37 weeks, abnormal conditions, congenital anomalies, born to mothers with complications of labor and delivery, or assisted vaginal deliveries
- ^c Estimated PBB is at the time of conception and calculated from an elimination model that adjusts for the mother's body mass index at enrollment, smoking history, and pregnancy and breastfeeding histories.
- ^d Enrollment PBB models adjust for the mother's body mass index at enrollment and excludes infants born to mothers who either reported being a smoker at enrollment or being pregnant since 1973.
- ^e Enrollment PCB models adjust for maternal smoking status, parity, education, and age at delivery.

Table 4
Adjusted odds ratios and 95% CIs for Apgar Scores below the median stratified by age at exposure (all infants)^a

Models	Apgar Scores at 1 minute						Apgar Scores at 5 minutes					
	<9 years at exposure			9 years at exposure			<9 years at exposure			9 years at exposure		
	N	OR	95% C. I.	N	OR	95% C. I.	N	OR	95% C. I.	N	OR	95% C. I.
Estimated PBB ^b (ppb)												
1	76	1.00	-	67	1.00	-	76	1.00	-	67	1.00	-
>1 - <2.5	115	3.03	(1.29 - 7.08)	72	1.60	(0.58 - 4.42)	115	3.93	(1.15 - 13.42)	72	1.73	(0.56 - 5.31)
2.5	106	3.54	(1.48 - 8.47)	87	1.82	(0.72 - 4.63)	106	3.70	(1.06 - 12.87)	87	1.75	(0.60 - 5.06)
Enrollment PBB ^c (ppb)												
1	70	1.00	-	57	1.00	-	70	1.00	-	57	1.00	-
>1 - <4	123	2.41	(0.98 - 5.93)	76	0.84	(0.33 - 2.12)	123	2.12	(0.66 - 6.76)	76	1.25	(0.40 - 3.95)
4	132	3.33	(1.37 - 8.12)	97	0.94	(0.41 - 2.15)	132	2.66	(0.84 - 8.44)	97	1.19	(0.41 - 3.48)

^a Apgar scores below the median are <8 for 1 minute and <9 for 5 minutes; all models adjusted for infants born to the same mother

^b Estimated PBB is at the time of conception and calculated from an elimination model that adjusts for the mother's body mass index at enrollment, smoking history, and pregnancy and breastfeeding histories.

^c Enrollment PBB models adjust for the mother's body mass index at enrollment and excludes infants born to mothers who either reported being a smoker at enrollment or being pregnant since 1973.