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A State of the Science Review of Human Health Effects of the Michigan Polybrominated Biphenyl Contamination after Five Decades

Susan S. Hoffman,[1] John A. Kaufman,[1]* Robert B. Hood,[1,2] Tamar Wainstock,[3] Kathleen Hartnett,[4] Hillary Barton,[1] Melanie A. Pearson,[5] Metrecia L. Terrell,[1] and Michele Marcus[1,5]*

[1]Department of Epidemiology, Emory University, Atlanta, Georgia, USA
[2]Division of Epidemiology, The Ohio State University, Columbus, Ohio, USA
[3]Department of Public Health, Faculty of Health Sciences, Ben Gurion University of the Negev, Beersheba, Israel
[4]Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA
[5]Department of Environmental Health, Emory University, Atlanta, Georgia, USA

Background: The Michigan Polybrominated Biphenyl (PBB) Registry, followed since 1976, was created after a 1973 chemical manufacturing mistake. The flame retardant PBB was accidentally mixed into animal feed and distributed to Michigan farms for nearly a year, exposing farm residents and animal product consumers.

Objective: We synthesized knowledge to date on health effects of PBB exposure within the Michigan PBB Registry and describe research findings in the context of literature on other persistent organic pollutants (POPs) and endocrine-disrupting chemicals (EDCs).

Methods: We reviewed literature published from 1973 to 2025 on human health effects of PBB following the Michigan contamination, using PubMed and Thompson Reuters (ISI) Web of Science databases. We excluded studies not in English; studies on exposures besides PBB; animal studies; reviews, abstracts, or letters to the editor; studies without a health outcome; and studies outside of Michigan or unrelated to the 1973 contamination. For each article, two researchers performed title and abstract screening, full article review, and data extraction.

Results: We included 79 publications out of 601 identified and screened. Early studies did not find many health outcomes associated with PBB, possibly because of methodological limitations. More recent studies on long-term and multigenerational impacts found an increased breast cancer risk, accelerated pubertal development and earlier menarche for girls exposed *in utero*, urogenital problems and slower pubertal development in boys exposed *in utero*, lower estrone 3-glucuronide and follicle-stimulating hormone among women exposed in childhood, and increased miscarriage risk among daughters of exposed women. Epigenetic and metabolomic research reported altered pathways related to estrogenic effects and immune function as well as the epigenetic alterations of spermatogenic cells.

Discussion: This unique community–academic partnership has produced insights into multigenerational consequences of EDC/POP exposures across the life course. The findings from this cohort underscore the broader relevance of critical windows of vulnerability, particularly during fetal development and childhood. https://doi.org/10.1289/EHP15012

Introduction

Brominated flame retardants (BFRs) are chemicals added to various consumer products, including fabrics, foams, furniture, and electronics, to reduce flammability.[1] BFRs that are persistent organic pollutants (POPs), including polybrominated biphenyls (PBBs)[2] and polybrominated diphenyl ethers (PBDEs),[3] have generally been phased out of production due to health concerns. Toxicological and epidemiological studies of BFRs have demonstrated potential effects on thyroid function,[2,4,5] reproductive development,[4–8] fertility,[9,10] birth outcomes,[11] metabolic function,[12] neurodevelopment,[13,14] and cancer.[15] In its most recent assessments, the International Agency for Research on Cancer (IARC) classified PBBs and the still widely used BFR tetrabromobisphenol-A as "probably carcinogenic to humans."[16,17] Exposure to persistent BFRs remains widespread globally because of their resistance to environmental degradation or metabolism, with some having biological half-lives measuring a month to over a decade.[18–20] Further, replacement BFRs ensure continued ubiquitous exposure to similar chemicals, with emerging evidence suggesting they may also be harmful.[17,20,21]

BFRs may impact health through similar mechanisms as other halogenated POPs, such as polychlorinated biphenyls (PCBs), as has been suggested by research on dioxin-like compounds.[22] PBBs and other BFRs may cause health effects by mimicking or blocking the actions of endogenous hormones. Studies in rat[23,24] and zebrafish[7] animal models have provided evidence that BFRs are endocrine-disrupting chemicals (EDCs).[21,25] EDCs may interfere with the uptake, transport, binding, metabolism, or elimination of natural hormones.[26] These chemicals can act on nuclear, steroid hormone, and neurotransmitter receptors, as well as through enzymatic pathways, changes in DNA methylation, and histone modifications.[27] BFRs such as PBBs and PBDEs may interfere directly with receptor signaling or may activate other signal transduction pathways like the aryl hydrocarbon receptor (AhR). An *in vitro* study found that several BFR mixtures, including FireMaster BP-6, activated the AhR, though this activity may be partly due to BFR mixture contaminants such as polybrominated dibenzo-*p*-dioxins and dibenzofurans.[28,29]

Background on the Michigan Polybrominated Biphenyls Registry

In 1973–1974, a commercial PBB mixture (FireMaster) was erroneously distributed to livestock feed mills across Michigan instead of a nutritional supplement (NutriMaster).[30] The highly lipophilic mixture was added to livestock feed and consumed by millions of cows, chickens, geese, and hogs at farms across Michigan. Ultimately, PBB was ingested throughout Michigan by consumers of dairy, meat, and egg products from these farms.[31] Farmers who used the PBB-contaminated feed documented problems in dairy cows, including decreased appetite and milk production; weight loss; lameness; abnormalities in skin, hair, and hooves; birth defects; and premature death.[32] Studies of affected cattle found increased rates of sterility, reduced milk production,[30] pregnancy complications, and increased rates of stillbirth.[32]

The cause of livestock problems in Michigan was not identified as PBB until May 1974. By then, PBB had been distributed to farms throughout the state.[33] Between mid-1973 and 1974, before the affected animals were identified and highly contaminated farms were quarantined by the Michigan Department of Agriculture (MDA), an estimated 6.5 million residents consumed PBB through animal products.[34,35] In May 1974, the MDA set an initial "tolerance level" of 1 ppm of PBB in meat, dairy, and eggs, which by November 1974 was lowered to 0.3 ppm until 1977, when the sale of PBB-sickened animals and their products was no longer allowed.[31] These regulatory responses meant that

although the highest exposures occurred in 1973–1974, exposures via animal products continued until 1977.[34] A 1978 representative cross-sectional statewide study of Michigan residents detected PBB in 97% of 844 adipose samples [limit of detection (LOD) = 2 ppb] and in 70% of 1,681 serum samples (LOD = 0.2 ppb).[35] Another smaller survey of women who gave birth in 1976 ($n = 95$) found that >96% of sampled women from the Lower Peninsula ($n = 51$) and >43% of women from the Upper Peninsula ($n = 18$) had detectable PBB in their breast milk.[36,37]

PBB production in the United States ceased after this contamination event. However, PBB-153 (the most prevalent congener in FireMaster) was detected in 77% of sampled Americans in the 2013–2014 National Health and Nutrition Examination Survey (NHANES; LOD = 0.001 ppb).[38,39] In a study examining serum PBB-153 concentrations in F0 (first-generation participants in the Michigan PBB Registry) and F1 (second-generation participants in the Michigan PBB Registry) Michigan residents 40 y of age after the disaster (samples collected in 2012–2014; 7–88 y of age), PBB levels continued to be significantly higher [male geometric mean (GM): 45.2 ng/g lipid; female GM: 16.4 ng/g lipid] than the average sampled through NHANES (male GM: 3.2 ng/g lipid; female GM: 2.2 ng/g lipid),[40] and 60% had levels higher than the 2003–2004 NHANES 95th percentile. A study of 742 Black women born after the contamination event (born 1975–1989) in Detroit, Michigan, sampled in 2010–2012, detected PBB-153 in 89% of participants (LOD = 0.2 ng/g lipid; mean = 1.0 ng/g lipid).[41]

Before the Michigan disaster, little was known about the possible human health effects of BFRs. Early studies in exposed residents focused on acute health effects such as dermatological, liver, immune, and neurological impacts.[42] Later, as concern grew about the endocrine-disrupting potential of PBBs, studies focused on reproductive outcomes. PBB can cross the placenta and concentrate in breast milk[43]; therefore, children born to exposed mothers would be exposed *in utero* and throughout early infancy. These individuals were exposed during critical developmental windows and were specifically studied to determine whether any PBB-associated health outcomes differed from those who ingested PBB as adults.

Fifty years after the Michigan PBB disaster, we are still learning about its long-term effects, particularly in the second generation exposed prenatally. Although production has been discontinued, many Michigan residents and their offspring are still experiencing the impacts of this contamination[40] and seeking answers.[44] In addition, research on PBB can inform our understanding of health impacts of other EDCs used today. The unique circumstances of this contamination event, including high exposure to a diverse population during a defined time period, allow researchers to investigate the health effects of exposure during specific life stages and among specific vulnerable subpopulations. In this paper, we review the subacute, long-term, and multigenerational human health effects of PBB on those directly impacted by the Michigan disaster. We also provide an overview of recent research exploring biological pathways associated with PBB exposure and possible mechanisms for PBB-associated health outcomes. Finally, we highlight areas for future research and the applicability of the registry to ongoing work in understanding how EDCs and POPs impact human health.

Study Populations

The Michigan Long-Term PBB Study cohort was established in 1976 by the Michigan Department of Public Health [MDPH, subsequently the Michigan Department of Community Health (MDCH), from 1996 to 2015 and the Michigan Department of Health and Human Services (MDHHS) since 2015] with funding from the US Centers for Disease Control and Prevention (CDC) and the National Cancer Institute (NCI).[42] The purpose of establishing this registry was to provide long-term surveillance of the possible health effects of PBBs, with an emphasis on monitoring cancer incidence and other chronic, delayed, or multigenerational health outcomes.[42] Since 1996, researchers at Emory University, in collaboration with the MDCH/MDHHS, have maintained and expanded the original cohort, referred to herein as the Michigan PBB Registry. Since 2011, Emory researchers have partnered with multiple community and governmental organizations (Pine River Superfund Citizen Task Force, PBB Community Advisory Board, Mid-Michigan District Health Department, MDHHS) to pursue research questions and priorities of exposed Michigan residents. The registry contains records and documented exposures on ~7,500 individuals,[40] including children and grandchildren of the original participants,[45] spanning five decades.

The population enrolled in the Michigan PBB Registry includes three groups: *a*) former workers of the chemical manufacturing plant where PBB was produced, with occupational exposure via inhalation and dermal absorption in addition to ingestion of contaminated farm products; *b*) the first generation (F0) of exposed Michigan farm residents and consumers of farm products who were children or adults in 1973, primarily exposed through ingestion of contaminated products; and *c*) subsequent generations born to PBB-exposed parents, potentially exposed to epigenetic modifications of the parental genome and exposed to PBB *in utero* and/or through breastfeeding, during critical windows of development (F1/F2). Figure 1 depicts the life-course and exposure timelines for the F0, F1, and F2 generations.

Chemical workers (dermal and inhalation exposure). The Velsicol Chemical Corporation plant, formerly known as the Michigan Chemical Corporation plant, in St. Louis, Michigan, was the source of the PBB contamination.[30] The company produced several chemicals there, including PBB, the organochlorine pesticide dichlorodiphenyltrichloroethane (DDT), and numerous other halogenated compounds, including POPs, from 1970 until 1974.[46] Several early studies included chemical workers as a subgroup of interest, assuming they were exposed over a more extended period than farm product consumers and through different routes, i.e., dermal or inhalation.,[42,47–54] Early studies suggested that chemical workers had higher PBB body burdens than farmers. A 1978 study by researchers from the Mount Sinai School of Medicine found a median serum PBB level in 55 chemical workers of 9.3 parts per billion (ppb) in comparison with 3.9 ppb in 283 residents of highly contaminated state-quarantined Michigan farms.[47] A study by MDPH[48] found a median serum PBB level of 20 ppb in 29 male workers involved in PBB production, in comparison with a median of 4 ppb in 83 male farm workers. The original PBB cohort enrolled 251 former chemical plant workers,[42] though some studies did not include these individuals due to their multiple chemical exposures (e.g., organochlorine pesticides).[47] In 2012, at the request of former chemical workers and their families, Emory and the MDCH/MDHHS reached out to former workers and provided opportunities to participate in ongoing studies on the health effects of PBB. Many have reenrolled and participated in ongoing research.[40]

F0 cohort members, exposed via ingestion of contaminated food and/or inhalation or dermal absorption from handling contaminated feed. From July 1976 to December 1977, the MDPH recruited participants including quarantined and nonquarantined farm residents, farm product consumers, and children (with parental consent).[42] At enrollment, each participant completed a questionnaire including demographic and medical information ($n = 3,877$, or 94% of 4,125 invited). A blood sample was collected from those who provided consent and included 94% (3,639/3,877) of enrolled participants. These samples were analyzed for PBBs by gas chromatography with electron capture

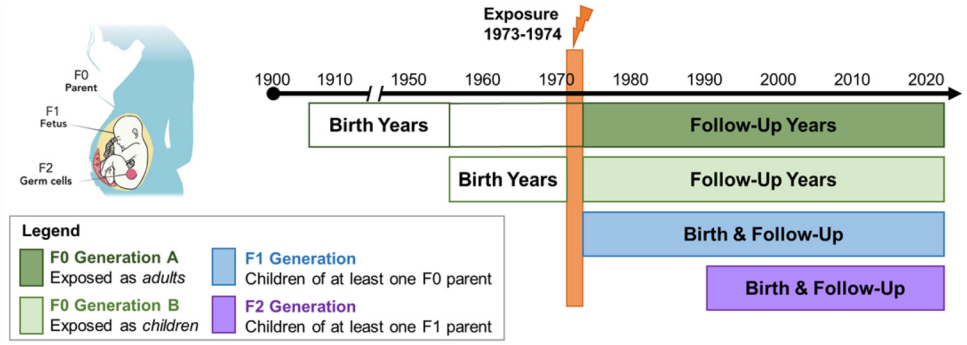

Figure 1. Life course timeline for F0, F1, and F2 generations in the Michigan Polybrominated Biphenyl Registry.

detection. At enrollment, cohort members' serum PBB levels ranged from not detectable (<LOD of 1 ppb) to 1,900 ppb, with a median of 3 ppb.[42] Investigators updated health outcome information for these individuals and their enrolled offspring (see below) with questionnaires (1991–1993, 2000–2001), comprehensive telephone interviews (1997–1998, 2003–2006), and yearly updates mailed to participants that asked about new diagnoses and births since the last update (2–13 y after enrollment).

F1 and F2 cohort members, exposed via placenta and breastfeeding. PBB is transferred to the fetus across the placenta and to infants through breastfeeding.[43] Contaminated breast milk is an important source of exposure for children born after the PBB incident.[48,55] In 1978, the MDPH began enrolling any F1 children of the original F0 women in the cohort. Since 2012, the cohort has expanded to include the third generation (F2).[45]

Exposure Assessment

Research examining subacute effects (1973–1984). The first studies in this cohort relied on the initial PBB level measured at enrollment, although many studies used this value to confirm exposure and did not analyze outcomes by PBB levels. Instead, early studies used comparison groups that were assumed to be unexposed, such as Wisconsin farmers, or to have lower exposure, such as consumers of farm products.

Research examining long-term effects (1984–2025). Later research stratified by serum PBB concentrations. In 2000, Blanck et al.[56] created an elimination model to estimate PBB levels at times of biological interest, including maternal levels at conception to estimate *in utero* exposure. The 2000 model used an ordinary least squares method to predict PBB serum levels, using data from 380 women with an initial PBB level >2 ppb (twice the LOD) and at least two PBB measurements.[56] In 2008, researchers refined this using general linear mixed models.[57] Higher BMI and older age at exposure were marginally associated with a slower elimination rate, and smoking was associated with a faster rate.[57] PBB was also eliminated faster among women who breastfed between serum PBB measurements, suggesting lactational transfer of PBB.[57] There was a high correlation between predicted and measured PBB-153 concentrations ($r = 0.93$).[57] Recently, researchers further refined the elimination model by incorporating more recent serum samples.[58] Higher BMI, younger age at initial exposure, and higher gravidity (possibly because of weight gain during pregnancy that allowed for increased PBB storage and retention of adipose tissue[59]) were associated with a slower elimination rate, whereas smoking and breastfeeding were associated with a faster elimination rate.[58]

Methods

Literature Search

We performed a systematic search of the literature on health effects of PBB within the population exposed following the Michigan PBB contamination crisis. To ensure the rigor of our work, we followed PRISMA reporting guidelines for scoping reviews.[60]

We systematically searched the PubMed and Thomson Reuters (ISI) Web of Science databases to identify all studies on human health effects of PBB in Michigan residents published after 1973, including articles up to 17 January 2025. We used the search terms "polybrominated biphenyl* AND Michigan" and included all peer-reviewed articles that presented new data on human health outcomes resulting from the Michigan PBB disaster. We limited the results to research in English and in human populations. In addition to the database searches, we manually reviewed references of eligible papers and selected articles.

All citations were imported into Covidence (2022; Veritas Health Innovation, Melbourne, Australia) for abstract review, full-text review, and extraction. We first conducted a title and abstract screening, with two researchers screening each article. Articles were excluded if they were *a*) not written in English, *b*) focused on a pollutant other than PBB, *c*) animal studies, *d*) not researching those exposed as a result of the 1973–1977 Michigan contamination and residing in Michigan, *e*) reviews, abstracts, or letters to the editor (i.e., not an original research article), or *f*) not focused on a health outcome. We then performed a full-text review, with two researchers reviewing each article using the same criteria for exclusion. Any disputes were settled by a third coauthor on the project. The selection process is detailed in Figure 2. We then extracted relevant data from each article on the title, authors, year of publication, year the data were collected, study design, possible conflicts of interest, population description, inclusion criteria for the study, exclusion criteria, total number of participants, source population, whether adults or children, timeline (generation), how the outcome was measured, outcome of interest, how the exposure was operationalized (e.g., serum measurement, comparison group), authors' conclusion, and any additional notes or comments on the article deemed relevant to the review.

We did not complete a formal risk of bias assessment, as a widely accepted tool for evaluating and categorizing bias risk in observational studies does not currently exist.[61] Instead, we discuss potential sources of bias within the relevant subsections of the "Discussion" section.

Results

We identified 594 records from PubMed and Web of Science databases and 7 from citation lists (total $n = 601$; see Figure 2). After performing title and abstract reviews for these 601 records, we identified 115 publications that focused on PBB exposures resulting from the 1973–1974 agricultural contamination in Michigan, published from 1975 to 2025, for full-text review. Based on the full-text review, 36 of these did not meet the inclusion criteria and are not included in our results. Reasons for exclusion included focusing on an exposure other than PBB ($n = 18$), a study in nonhuman animals ($n = 9$), a study outside Michigan ($n = 8$), and being a publication form other than a research paper (i.e., a review, abstract, or letter to the editor; $n = 1$).

We summarize our findings in four sections: *a*) acute and subacute effects in the F0 generation (1975–1987; Table 1; Table 2), *b*) long-term effects in the F0 generation (1990–2025; Table 3; Table 4), *c*) effects in the F1/F2 generations (Table 5; Table 6), and *d*) recent epigenetic and metabolomic findings (Table 7; Table 8). Tables 1, 3, 5, and 7 summarize the findings of these four sections by health outcome, and Tables 2, 4, 6, and 8 present details for each study discussed in these sections.

Acute and Subacute Effects in the F0 Generation: Findings from Early Studies (Published 1975–1987)

Most early publications were produced by researchers from Mount Sinai School of Medicine (now Icahn School of Medicine at Mount Sinai), who undertook a statewide study of the impacts of PBB exposure on Michigan's population in 1978–1979 (Table 1). A total of 1,738 individuals 1–89 y of age from six study locations across the state were recruited and completed questionnaires and a clinical examination; 1,651 had serum PBB measured.[42] Although these studies documented a high prevalence of symptoms among various highly exposed groups, the absence of significant dose–response relationships led to the dismissal of health-related liability claims against Velsicol Chemical Company.[31]

A series of published analyses presented many unadjusted statistical comparisons [largely 2×2 chi-square tests and *t*-tests (two-sided and paired)]. Most comparisons did not use measured PBB values but compared symptom severity across various groups, such as residents of quarantined and nonquarantined Michigan farms, consumers of products from quarantined and nonquarantined Michigan farms, chemical workers involved in PBB production and those not working with PBB, and unexposed Wisconsin farm residents (see Table 2 and the outcome-specific sections below for group comparisons within each study). It is likely that all of the Michigan groups were exposed to PBB from eating contaminated animal products (PBB was detected in all groups) and comparisons between these groups likely masked associations that may have existed.[47] The Michigan farm residents and consumers had similar PBB distributions, but those who resided on quarantined farms or consumed food from quarantined farms had higher PBB concentrations.[78] Using comparison groups as proxies for PBB exposure precluded determinations of exposure–response relationships.

Several publications provide descriptive summaries of the prevalence of various self-reported symptoms,[46,49,78] whereas others focused on specific health outcomes through sets of tests or targeted self-reported symptoms; we focus our discussion on the latter because they present more methodological detail. Besides the Mount Sinai studies, several publications were produced from different samples of affected communities, including the first studies from the Michigan PBB Registry and small occupational studies of chemical workers (Tables 1 and 2).

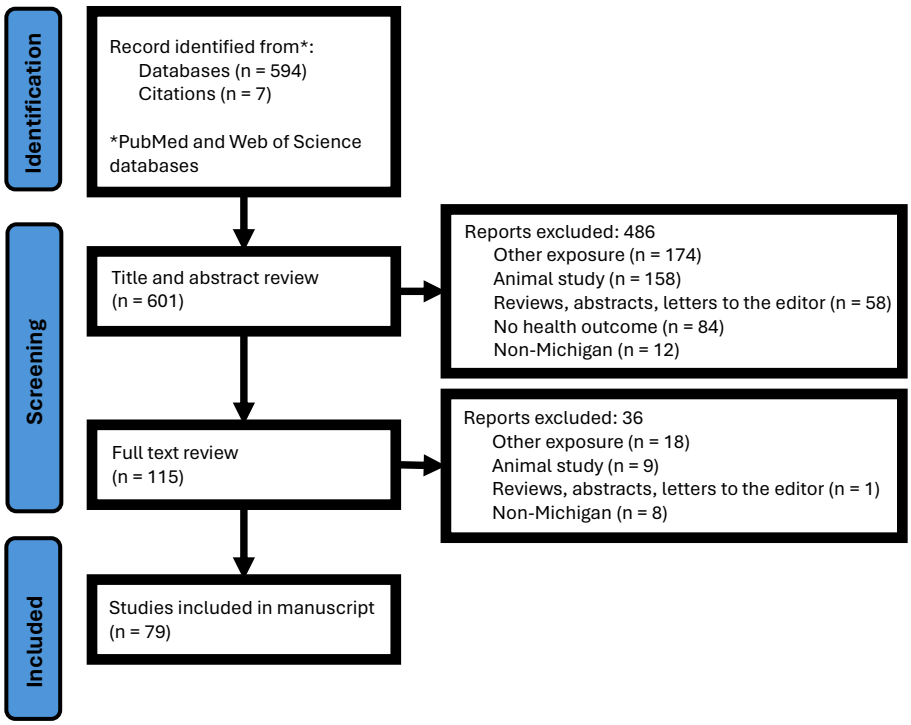

Figure 2. The selection process for articles after reviewing the PubMed and Thomson Reuters (ISI) Web of Science databases for all studies on human health effects of PBB in Michigan residents after 1973, including articles up to 31 October 2023. Articles were excluded if they *a*) were not written in English, *b*) focused on a pollutant other than PBB, *c*) were animal studies, *d*) were not researching those exposed as a result of the 1973–1977 Michigan contamination and residing in Michigan, *e*) were reviews, abstracts, or letters to the editor (i.e., not an original research article), or *f*) were not focused on a health outcome. Two researchers screened each article for both screening steps. This figure was adapted from PRISMA reporting guidelines for scoping reviews.[60] Note: PBB, polybrominated biphenyl.

Table 1. Summary of investigated acute/subacute effects of PBB exposure in the F0 generation from studies published in 1978–1987, 5–14 y after the contamination event.

Health outcome	Association	Literature summary	Citations
Liver function	−	Two Mount Sinai studies comparing MI residents to WI residents showed no significant difference between serum PBB levels and liver function tests.	49, 63, 65
Dermatological problems	+	After initial exposure, significant acute dermatological problems in MI residents were reported at a much higher frequency compared with WI residents.	46, 51, 66
Immunological function	±	A series of studies conducted at Mount Sinai comparing MI residents to WI and NY residents showed an altered immune response in adults; however, these results were not consistent in other studies.	33, 42, 52, 70–72
Male reproductive effects	−	No differences were noted in sperm quality or in testosterone, luteinizing hormone, or follicle-stimulating hormone.	53
Neurological symptoms	−	Generally, studies did not find an association between PBB levels and neurological function, and differences that were identified were often thought to be a result of confounding bias due to the personal and financial losses caused by the PBB contamination.	46, 64, 73–75
Thyroid disease	±	One study found an increased prevalence of thyroid disease in MI residents compared with WI residents, another found increased hypothyroidism and altered thyroid hormone levels in MI chemical workers compared with other occupations, and a third study found no significant associations between PBB levels and thyroxine in either children or adults.	46, 65, 76
Diabetes	−	There was no significant difference in diabetes rates by PBB level in unadjusted analyses.	42, 46
Cancer	−	There was no significant association between cancer and PBB exposure, however, due to the long latency period of the disease, enough time might not have elapsed to detect a significant difference.	42, 77
Overall mortality	−	There was no significant difference between overall mortality comparing workers with routine PBB exposure and those without PBB exposure.	78
Adverse birth outcomes	−	There was no difference in infant mortality in counties with and without a high proportion of quarantined farms.	79
Impact of PBB on children	−	There were generally null findings in studies of children exposed to PBB in infancy through adolescence; however, this could be attributed to sample size and study design.	80–84

Note: + indicates an association (any direction) between PBB and the outcome; ± indicates mixed results; − indicates null results. DDE, dichlorodiphenyldichloroethylene; F0, first generation exposed through diet and occupation; MI, Michigan; NA, not available; NY, New York; PBB, polybrominated biphenyls; WI, Wisconsin.

Liver Function

Mount Sinai studies. A study conducted in 1977 compared adult (18+ y of age) Wisconsin dairy farm residents ($n = 141$) to adult (18+ y of age) Michigan residents ($n = 614$, quarantined farm residents and consumers).[62] Michigan residents had a higher prevalence of abnormal liver function markers, i.e., levels of the enzymes serum glutamic-oxaloacetic transaminase (SGOT >41 IU/L; 10.7% vs. 2.8%, $p < 0.005$) and serum glutamic-pyruvic transaminase [(SGPT) >45 IU/L; 11.1% vs. 2.8%, $p < 0.005$]; however, *t*-tests for differences in means of SGOT and SGPT were not statistically significant. Among Michigan participants with measured serum PBB levels ($n = 364$), there was no significant association between liver markers and PBB based on simple univariate linear regression, and increased PBB levels were not associated with an increased prevalence of abnormal liver function tests based on chi-square tests. Similar results were found in a parallel cross-sectional study of 1,029 Michigan residents.[49]

Additional studies. Two other early studies examined liver abnormalities but did not assess these outcomes by PBB level. The first, conducted in 1976, studied a selected sample of 46 quarantined farm residents (no reference group and no age range provided) with incapacitating health complaints (serum PBB range 1–180 ppb, mean = 14 ppb).[63] The most prevalent finding from a physical examination was hepatomegaly (78%), although liver enlargement was primarily mild and not associated with tenderness or stigmata of chronic liver disease. In a later study published in 1981,[50] researchers found high rates of hepatomegaly in 4 out of 23 farmers from predominantly quarantined farms (17%; age 16–59 y) and 2 out of 28 chemical workers known to have worked with PBB directly (7%). In another study in 1982 examining PBB impacts on various clinical markers, researchers found that although some liver function markers, such as alkaline phosphatase, SGOT, SGPT, and lactic dehydrogenase (LDH), were statistically significant in certain years or sex groups, there was no consistent or meaningful pattern reported.[81]

Dermatological

Three years after the contamination event, initial studies noted prevalent dermatological problems (including unexplained rash, acne, increased sun sensitivity, burning sensation, darkening or thickening of the skin, discoloration or deformity of the finger or toenails, and slower or poorer healing of cuts) among exposed Michigan residents.[46,49,51] A more detailed comparison of the prevalence of skin problems between Michigan farm residents ($n = 359$ quarantined, $n = 199$ nonquarantined), Michigan chemical workers ($n = 10$ PBB handlers, $n = 43$ not working with PBB), and Wisconsin farm residents ($n = 149$) found that chemical workers had the highest prevalence (70%) and Wisconsin residents had the lowest (18%).[64] However, differences were not tested by PBB level. This study noted that cutaneous effects aligned with animal studies of PBBs[118] and resembled "chloracne" found in human epidemiological studies of exposure to chlorinated biphenyls.[119,120]

Immunological

Mount Sinai studies. A series of studies with increasing sample sizes were conducted from 1976 to 1981 using biological markers of immune function. An early study found that a small group of Michigan farm residents ($n = 45$) had lower numbers and percentages of T and B lymphocytes, increased number of lymphocytes with no detectable surface markers, lower *in vitro* immune function, and impaired PHA-induced blastogenic response from a lower number and percent of T cells in the peripheral blood lymphocytes, indicating an altered immune response, in comparison with Wisconsin farm residents ($n = 46$), and New York City area residents ($n = 79$).[33] An extension of this study added 11 Michigan chemical workers and found alterations among the four workers who had handled PBBs but not among the seven who did not handle PBB.[52] A further extension included 336 Michigan farm residents, 117 consumers of Michigan farm products, and 75 Wisconsin dairy farmers examined in 1981 and found persistence in the reduced

Table 2. Research analyzing the acute/subacute effects of PBB exposure in Michigan residents.

Time since exposure event (1973)	Sample size and population	How the outcome is measured	Assessment of exposure	Main findings (from researchers)	Comments	Citations
Health outcome						
Exposure levels						
NA	190 MI women	Biological marker measurement	PBB levels in breast-milk	While looking at pesticide levels in the general MI population, researchers found PBB in most of the MI breast-milk samples.	This study was not specifically designed to find PBB. Instead PBB was found while looking for other circulating chemicals.	36
NA	85 MI farm residents, chemical workers, and contaminated food consumers	Biological marker measurement	PBB serum levels, PBB in breast-milk, adipose tissue, cord blood, feces, and biliary fluid	This study showed PBB bioaccumulation in the body and showed that serum levels can model PBB in adipose tissue. Also showed PBB can cross the blood-placental barrier and be transferred through breast-milk.	Groundwork research in the complex ways PBB interacts with the human system.	48
NA	313 MI women	Biological marker measurement	PBB serum levels, PBB in breast milk and cord blood	Found that maternal PBB serum levels were higher than PBB found in cord serum and breast milk. The mother's PBB serum levels can estimate both breast milk and cord blood levels.	Groundwork for using PBB serum as a model for reproductive studies.	43
NA	984 MI farm residents and chemical workers; 229 WI farm residents	Biological marker measurement	Using comparison group (WI farm residents), PBB levels at enrollment	Comparing serum DDE levels to PBB levels and demonstrated that DDE is a low-level chronic exposure whereas PBB was a recent, concentrated, interim exposure.	Groundwork study demonstrating that observed PBB is linked to the PBB accident from the Michigan chemical company.	47
Liver function						
3–4 y: The MI sample was collected in 1976 and the WI in 1977	614 MI adults (18+ y of age); 141 WI adults (18+ y of age)	Self-reported signs and symptoms, Biological markers measurement	Used comparison group (WI farm residents)	There was a greater prevalence of abnormal SGPT and SGOT amount MI farmers residents, tentatively linked to PBB exposure.	This research used Wisconsin Farm residents as a comparison instead of stratifying results by serum PBB levels.	62
3 y: Information was collected in 1976	55 MI chemical workers; 204 MI residents (no ages provided)	Self-reported signs and symptoms, clinically defined outcome	Used comparison group (MI residents); PBB serum levels at enrollment	Found no significant difference between the MI chemical workers and MI residents.	This research relies on comparison groups and not serum PBB levels.	51
3 y: Information was collected in 1976	1,029 MI farmers and consumers of farm products (no ages provided)	Clinically defined outcome	Used comparison group (MI residents); PBB serum levels at enrollment	Found liver abnormalities across MI residents	Compared across different groups of MI residents (farmers, chemical workers, consumers) and not by serum PBB levels	49
3 y: Information was collected in 1976	46 MI farm residents (no ages provided)	Clinically defined outcome, validated tests/scales, biological marker measurement	PBB serum levels at enrollment	Complete examinations were done on all participants, with the most prevalent finding being hepatomegaly, although liver enlargement was mild in the majority of cases	No clear comparison group described in this study.	63
Dermatological						
3 y: Information was collected in 1976	933 MI residents 1–70+ y of age; 229 WI residents 1–70+ y of age	Self-reported signs and symptoms, clinically defined outcome	Used comparison group (WI farmer residents)	Researchers found significantly higher prevalence of skin conditions in the MI group in comparison with the WI group.	This research used Wisconsin as a comparison instead of relying on PBB serum levels.	46
3 y: Information was collected in 1976	55 MI chemical workers; 204 MI residents (no ages provided)	Self-reported signs and symptoms, clinically defined outcome	Used comparison group (MI residents); PBB serum levels at enrollment	Compared with MI farmers, an increased prevalence of skin symptoms was observed in chemical workers	The research relies on a comparison group instead of serum PBB levels.	51

Table 2. (*Continued.*)

Time since exposure event (1973)	Sample size and population	How the outcome is measured	Assessment of exposure	Main findings (from researchers)	Comments	Citations
Unclear/9 y: study published in 1982	837 MI farmers and chemical company workers 1–18+ y of age; 228 WI farmers 1–18+ y of age	Self-reported signs and symptoms, clinically defined outcome	Used comparison group (MI residents); PBB serum levels at enrollment	Find that PBBs are implicated in increased prevalence of halogen acne, hair loss, skin redness, skin peeling and scaling, itching, increased sweating, and increased growth of fingernails and toenails	Analysis focused on comparing results to WI farmers, although mean serum PBB for each group was reported.	64
3 y: Information was collected in 1976	1,029 MI farmers and consumers of farm products (no ages provided)	Clinically defined outcome	Used comparison group (MI residents); PBB serum levels at enrollment	Associated PBB exposure with dermatological issues.	Compared across different groups of MI residents (farmers, chemical workers, consumers) and not by serum PBB levels	49
Immunological						
3 y: Information was collected in 1976	45 MI; 79 NY; 46 WI residents (no ages provided)	Biological marker measurement	Using comparison group (WI and NY residents), PBB Serum levels at enrollment	Found no consistent correlation with serum PBB and altered lymphocytes, however NY and WI residents had no similar lymphocyte abnormalities.	Small sample size and used non-MI residents as a comparison; however, researchers did stratify by serum PBB levels	33
Unclear/6 y: study published in 1979	66 MI farm residents and chemical workers; 46 WI farmers (no ages provided)	Biological marker measurement	Using comparison group (WI residents), PBB Serum levels at enrollment	Found decreased number of T-lymphocytes with no detectable surface markers and altered lymphocyte function associated with PBB exposure.	This was a follow-up study from Bekesi (1978) focusing on serum PBB concentrations and abnormal lymphocytes.	52
Unclear/6 y: study published in 1979	45 MI; 79 NY; 46 WI residents (no ages provided)	Biological marker measurement	Using comparison group (WI and NY residents), PBB Serum levels at enrollment	T and B lymphocyte subpopulations of peripheral blood lymphocytes showed evidence of functional defect.	It was not clear how the NY participants contributed to this study. Research used WI comparison group and did not include serum PBB concentrations.	65
Unclear/14 y: study published in 1987	336 MI farmers; 117 MI consumers; 75 WI farmers (no ages provided)	Biological marker measurement	Using comparison group (WI farmers), PBB serum levels at enrollment	Study found a persistence in reduced T lymphocytes and increased null cell values.	This research did not provide clear statistical analysis methodology.	66
1 y: survey conducted in 1974	3,639 MI farmers, consumers, chemical workers, and general population (1–89 y of age)	Biological marker measurement	Serum levels at time of data collection	No associations were found between serum PBB levels and symptom prevalence rates; No statistically significant differences in lymphocyte number or function were noted.	This research had limited details on their statistical analyses; The reference group used were participants with the lowest serum PBB concentrations instead of participants with levels below the limit of detection.	42
Unclear/6 y: study published in 1979	107 MI residents; 9 health department staff (no ages provided)	Biological marker measurement	Serum levels at time of data collection	Researchers found no association between PBB exposure level and total leukocyte count.	This research was limited by a small sample size when stratified by PBB level.	67
Male reproductive effects						
4 y: samples collected in 1977	104 MI male dairy farmers, chemical workers, and graduate students (20–60 y of age)	Biological marker measurement	Using comparison group (unexposed graduate students)	Analyses found no differences in the distribution of sperm counts, motility, or morphology.	Did not use serum PBB levels when analyzing the results	53

Table 2. (*Continued.*)

Time since exposure event (1973)	Sample size and population	How the outcome is measured	Assessment of exposure	Main findings (from researchers)	Comments	Citations
Neurological						
3 y: Information was collected in 1976	933 MI residents 1–70+ y of age 229 WI residents ages 1–70+ y of age	Self-reported signs and symptoms, clinically defined outcome	Used comparison group (WI farmer residents)	Found higher prevalence of neurological symptoms in MI participants compared with WI participants	Analysis relies on a comparison group (WI residents) and not serum PBB levels.	46
3 y: Information was collected in 1976	1,029 MI farmers and consumers of farm products (no ages provided)	Clinically defined outcome	Used comparison group (MI residents); PBB serum levels at enrollment	Found a prominent indication of neurologic syndrome, specifically tiredness and fatigue	Compared across different groups of MI residents (farmers, chemical workers, consumers) and not by serum PBB levels	49
Unclear/6 y: study published in 1979	42 MI farmers (mean age: 41.4 y)	Validated tests/scales	Comparison group (hospital volunteers), PBB levels in adipose tissues	Found no correlation between PBB adipose levels and cognitive test performance, however persons exposed to PBB did less well on recall, short-term memory, concentration, and cognitive flexibility in uncontrolled comparisons to hospital volunteers	Small sample size and using hospital staff from MI as the comparison group that were not tested for PBB	68
Unclear/8 y: study published in 1981	25 MI chemical workers (mean age: 38.3 y); 21 MI farm residents	Validated tests/scales	Using comparison group (MI farm residents), PBB levels in adipose tissue	Adipose PBB levels showed no correlation with memory performance.	Small sample size; assumed that chemical workers were more had higher levels of PBB than farmers and used farmers as the comparison group	54
4 y: data collected in 1977	18 MI children 4–6 y of age	Validated tests/scales	Using comparison group (age appropriate mean), PBB levels in adipose tissue	PBB cohort children were within the normal range in all areas assessed, however, there was an inverse relationship between PBB in adipose tissue and some developmental tasks.	This study tried to do a match case-control, however, all of the MI children in the control group had high levels of serum PBBs.	69
4 y: data collected in 1977	19 MI children 2–4 y of age	Validated tests/scales	PBB serum levels at enrollment	The results suggested an inverse relationship between serum PBB levels and some developmental abilities in young children.	The study had a small sample size.	70
Unclear/6 y: study published in 1979	46 MI farm residents (no ages provided)	Clinically defined outcome, validated tests/scales, biological marker measurement	PBB serum levels at enrollment	Researchers found that patients with known exposure to PBBs and incapacitating health care complaints, there was a high prevalence of hepatomegaly (72%), sensory neuropathies (41%), and reactive depression (67%).	No clear comparison group described in this study.	63
1 y before −3 years after: data collected from 1972 to 1976	644 MI and 153 WI farm residents 0 to >50 y of age	Validated tests/scales	Used comparison group (WI farm residents); PBB serum levels at enrollment	Preliminary analyses indicate many neurological symptoms occurring during the PBB exposure period (1972–1976) among MI farmers.	Instead of using the PBB serum levels, the papers compared MI farmers to WI farmers and MI men compared with MI women.	71
1 y before −3 y after: data collected from 1972 to 1976	623 MI and 153 WI farm residents 0 to >50 y of age	Validated tests/scales	Used comparison group (WI farm residents)	In MI (particularly among males), those who exhibited the most marked symptoms tended to show diminished performance as assessed by special tests.	Researchers compared results to WI residents. Although they took PBB serum samples, they used them only to confirm exposure.	72
4 y: data collected in 1977	53 MI children (33 exposed, 20 control; mean age = 3 y)	Self-reported signs and symptoms, clinically defined outcome, validated tests/scales	Used comparison group (unexposed MI children), PBB levels in adipose tissue	This study found no relationship between PBB and neurological development issues in MI children.	This study used a control group of MI children and assumed that they were unexposed to PBB.	73

Table 2. (*Continued.*)

Time since exposure event (1973)	Sample size and population	How the outcome is measured	Assessment of exposure	Main findings (from researchers)	Comments	Citations
Thyroid function						
5 y: study conducted in 1978	35 cases and 89 controls from male MI chemical company workers (mean age = 35.9 y)	Biological marker measurement	Used comparison group	The cohort of male PBB workers was found to have a statistically significant increase in the prevalence of primary hypothyroidism.	The study included limited details on the working history of the participants and had a small sample size.	74
3 y: Information was collected in 1976	933 MI residents 1–70+ y of age 229 WI residents 1–70+ y of age	Self-reported signs and symptoms, clinically defined outcome	Used comparison group (WI farmer residents)	Although there was a higher prevalence of thyroid disease in MI residents, the difference was not statistically significant.	This research used WI as a comparison instead of relying on PBB serum levels.	46
Diabetes						
3 y: Information was collected in 1976	933 MI residents 1–70+ y of age; 229 WI residents 1–70+ y of age	Self-reported signs and symptoms, clinically defined outcome	Used comparison group (WI farmer residents)	No statistically significant difference in prevalence in diabetes between MI and WI residents	This research used WI as a comparison instead of relying on PBB serum levels.	46
1 y: survey conducted in 1974	3,639 MI farmers, consumers, chemical workers, and general population (1–89 y of age)	Biological marker measurement	Serum levels at time of data collection	In unadjusted analyses, there was no significant difference in the prevalence of diabetes between groups with different routes of exposure.	This research had limited details on their statistical analyses; The reference group used were participants with the lowest serum PBB concentrations instead of participants with levels below the limit of detection.	42
Cancer						
3 y: survey conducted in 1976	611 MI and 138 WI farm residents 18–36+ y of age	Clinically defined outcome, biological marker measurement	Used comparison group (WI farm residents)	This study found no significant association between elevated Carcinoembryonic Antigen (CEA) titers and PBB exposure, although the MI farm residents had an elevated CEA titers, generally.	The study used WI farmers as a comparison group instead of stratifying by PBB levels.	75
1 y: survey conducted in 1974	3,639 MI farmers, consumers, chemical workers, and general population (1–89 y of age)	Biological marker measurement	Serum levels at time of data collection	The prevalence of cancer was slightly higher among those who were exposed to PBB, although this difference was inconclusive.	This research had limited details on their statistical analyses; This analysis may have occurred too close to the contamination event for cancers to develop.	42
Overall mortality						
38 y before to 3 y after: mortality information was collected from 1935 to 1976	3,579 male chemical workers (no ages provided)	Clinically defined outcome	Used comparison group (other chemical workers)	No deaths occurred in chemical workers exposed to PBB.	The study lacked accurate exposure histories for the chemical workers and could not account for potential exposure to mixtures. There may not have been enough time passed in the PBB group to see a difference in overall mortality.	76
Birth outcomes						
7 y before to 8 y after: birth records pulled for 1966–1981	NA; general MI population sample from birth records	Clinically defined outcome	Used comparison group (Michigan Upper Peninsula counties)	This study found no significant difference between fetal death rates in MI residents of lower peninsula counties (exposed to PBB) and upper peninsula counties (not exposed to PBB).	This study assumed that those living in the upper peninsula of MI were either not exposed to PBB or only had low levels.	77

Table 2. (*Continued.*)

Time since exposure event (1973)	Sample size and population	How the outcome is measured	Assessment of exposure	Main findings (from researchers)	Comments	Citations
Various symptoms						
3–4 y: The MI sample was collected in 1976 and the WI in 1977	993 MI residents (28 ± 19 y of age) and 228 WI residents (33 ± 20 y of age)	Clinically defined outcome	Used comparison group (WI adults)	There were marked differences observed between the MI and WI participants that cannot be fully explained without considering exposure to PBB.	Researchers did look more closely at PBB serum levels, but the majority of the results focused on comparing groups, even after authors note that there isn't much of a difference in exposure in the MI-specific groups.	78
3–4 y: The MI sample was collected in 1976 and the WI in 1977	343 MI and 72 WI children 0–16 y of age	Clinically defined outcome, biological marker measurement	Used comparison group (WI children)	This study found that children exposed to PBB had an increased constellation of symptoms compared with those not exposed to PBB.	The study relied on a comparison group instead of using PBB levels. Only looked at symptom counts, not severity or impact to daily life.	79
3–4 y: The MI sample was collected in 1976 and the WI in 1977	292 MI children (9.3 ± 4.2 y) and 72 WI children (10.1 ± 4.2 y of age)	Self-reported signs and symptoms, clinically defined outcome	Used comparison group (WI children), PBB serum levels at enrollment	Clinical evaluations failed to correlate PBB exposure with frequent reports of ill health. This research found a negative correlation between PBB serum levels and prevalence of symptoms.	The study did not account for symptom severity or impact of symptom on daily life. Furthermore, this study omitted one outlier and relied on a comparison group and not the serum PBB levels.	80
Unclear/8 y: study published in 1981	51 MI farm residents and chemical workers (16–59 y of age)	Clinically defined outcome, biological marker measurement	Used comparison group (MI farmers), PBB levels in adipose tissue, feces, and bile	Study found no relationship between PBB levels and physical or laboratory abnormalities.	The study was not clear who the comparison group was; at times it appeared it was MI farmers, and at other times general population levels. This study also failed to stratify the population by PBB levels.	50
1–6 y: serum samples were collected from 1974 to 1979	749 MI residents (children and adults, no ages provided)	Biological marker measurement	PBB serum levels from 1974, 1977, 1978, and 1979	Researchers observed a slight negative association with bilirubin that was not statistically significant, and although some liver and kidney function markers showed significant associations in certain years or sex groups, no meaningful pattern was noted. Thyroxine levels were inversely associated with PBB levels in both adults and children, but this association was also not significant.	There is a lack of detail on the age of participants, which could have contributed to the inconsistent results reported by the researchers	81

Note: CEA, carcinoembryonic antigen; DDE, dichlorodiphenyldichloroethylene; MI, Michigan; NA, not available; NY, New York; PBB, polybrominated biphenyls; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; WI, Wisconsin.

Table 3. Summary of investigated long-term health effects of PBB exposure in the F0 generation in studies published from 1990 to 2023, 17–50 y after the contamination event.

Health outcome	Association	Literature summary	Citations
Thyroid function	±	Studies of thyroid function in people exposed as adults did not show a difference by PBB exposure level; however, a later study showed that those exposed as children (≤16 years of age) had an association between PBB and thyroid hormone levels.	85–87
Diabetes	−	There was no significant association between PBB exposure and the risk of developing Type II diabetes.	94
Liver function	+	A study focusing on cytochrome P-450 enzyme activity found that those exposed to PBB had reduced liver function.	95
Cancer	+	A positive association between PBB and breast cancer development has been identified. There has also been a dose-response relationship between PBB exposure and digestive system cancers and lymphoma. A positive, though statistically insignificant, association was found between PBB exposure and an abnormal Pap test result (cervical cancer screen).	96–98, 100, 101
Endometriosis	−	No relationship was identified between PBB exposure and the risk of endometriosis.	102
Menstrual function	+	Although there was no overall association between PBB and the menstrual cycle, when individual hormones were examined throughout the different phases, PBB was associated with lower estrone 3-glucuronide (E1-3G) levels and lower FSH levels during the follicular phase.	103, 106
Time to menopause	−	There was no statistically significant association between PBB and time to menopause.	107
Pregnancy outcomes	−	There was no association between PBB exposure and spontaneous abortion, hypertensive pregnancy disorders, gestational diabetes, and birth defects.	108, 109
Immune function	±	PBB was not associated with a composite of any autoimmune disorder, but there was an unadjusted positive association between rheumatoid arthritis in males.	110
Neurodevelopmental disorders	−	There was not a statistically significant association between PBB and attention-deficit/hyperactivity disorder among F0 participants exposed before 10 y of age.	111

Note: + indicates an association (any direction) between PBB and the outcome; ± indicates mixed results; − indicates null results. F0, first generation exposed through diet and occupation; FSH, follicle-stimulating hormone; MI, Michigan; PBB, polybrominated biphenyls; WI, Wisconsin.

T-cell and increased null cell values among Michigan participants in comparison with Wisconsin participants.[66] None of the four publications presenting these findings explained statistical methods in detail.[33,52,65,66]

Additional studies. Landrigan et al. compared lymphocytic function between two groups of selected individuals from the Michigan Long-Term PBB cohort based on their PBB levels 1 y after the contamination event.[42] The high-exposure group included 34 participants with PPB ≥300 ppb, and the low-exposure group included 56 participants with PBB <1–9 ppb. There was no association between PBB level and leukocyte count or lymphocyte function, except among children included in the study. Children with high exposure levels had higher numbers of circulating lymphocytes in comparison with other children ($p < 0.001$). Details on statistical methods were not included. Including individuals with comparatively high exposure levels of 1–9 ppb in the referent (rather than restricting to <1 ppb, for example) may have reduced the ability to detect differences between exposure groups.

Another publication analyzing data from this sample compared Michigan residents with high (PBB >300 ppb, $n = 41$), medium (PBB 1–11 ppb, $n = 59$) and low (PBB <1 ppb, $n = 7$) exposures and an unexposed control group of health department staff ($n = 9$) and found no association between exposure level and total leukocyte count (the group with high PBB levels had more children younger than 13 y of age, which elevated the group's mean), T and B lymphocytes, or mean spontaneous lymphocyte transformation.[67]

These findings partially contrast with those of the Mount Sinai investigations reported above,[42] which found an altered immune response among exposed Michigan participants in comparison with unexposed Wisconsin and New York controls, though no differences by PBB level within their Michigan sample. The Mount Sinai analyses also had larger comparison groups, possibly improving the ability to detect differences between groups.

Male Reproductive Effects

Mount Sinai studies. A study comparing semen collected 4 y after the contamination event from 52 PBB-exposed men (41 Michigan farmers and 11 chemical workers) to that of 52 male Michigan graduate students (presumed unexposed) reported no differences in sperm morphology, motility, or counts, or levels of testosterone, luteinizing hormone, or follicle-stimulating hormone (FSH).[53] The study reported no associations between serum PBB and sperm count or testosterone level; however, the data supporting these conclusions were not presented, and a description of the statistical methods was not provided.

Neurological

Mount Sinai studies. Neurological symptoms (including tiredness, headaches, somnolence, nervousness, depression, dizziness, paresthesia, blurred vision, muscle weakness, loss of balance, insomnia, perceptual change, and difficulty walking) were among the most common complaints in initial health surveys.[46,71,72] A comparison of the prevalence of neurological symptoms found an increasing trend in reported symptoms during each year from 1972 to 1976 among Michigan farm residents and farm product consumers ($n = 644$), in comparison with stable symptom prevalence among Wisconsin farm residents ($n = 153$); significant differences in symptom prevalence between the Michigan and Wisconsin groups were found, based on chi-square tests.[71] There were no statistically significant correlations between serum PBB levels and neurological test scores (embedded figures, block design, and digit symbol tests), though sample sizes were small due to age and sex stratification ($n < 20$ for most correlation tests). Another publication using these data reported statistically significant Pearson correlations between neurological performance test scores and markers of liver function, including SGPT ($r = -0.19$), bilirubin ($r = 0.23$), and total protein ($r = 0.20$), but not with PBB levels.[72]

Among randomly sampled Michigan residents in 1976, the prevalence of neurologic symptoms was 50% among quarantined farm residents, 40% among nonquarantined farm residents, 55% among consumers of quarantined farm products, 46% among consumers of nonquarantined farm products, and 30% among Wisconsin farm residents.[46] The authors suggested that these differences indicate that neurological symptoms may not have been solely psychosomatic effects of the trauma from significant personal and financial losses suffered by farmers, because consumers of quarantined and nonquarantined farm products (i.e., groups who did not experience the trauma of these

Table 4. Research on long-term effects of PBB exposure on the first generation (F0) of Michigan residents.

Time since exposure event (1973)	Sample size and population	How the outcome is measured	Assessment of exposure	Main findings (from researchers)	Comments	Citation
Health outcome						
Thyroid function						
31–42 years: Serum samples collected between 2004 and 2015	715 MI adults (51.19 ± 15.21 y of age)	Clinically defined outcome, biological marker measurements	Serum levels at time of survey/data collection	This study suggests that PBB was associated with thyroid function (free and total thyroxine and free and total triiodothyronine), particularly among those who were exposed as children or prenatally	Medication records were not available for all participants included in the analysis	82
31–33 y: Study conducted in 2004–2006	753 MI adults (18 to >60 y of age)	Clinically defined outcome, biological marker measurements	Serum levels at time of survey/data collection	This study found some evidence to support that PBBs were associated with thyroid disease and thyroid hormone levels (statistically insignificant)	This study had limited sample size for the sample with thyroid disease limiting the power of the results	83
24 y: Questionnaire administered in 1997	3,333 MI cohort members age-matched case control study (no age breakdown provided)	Clinically defined outcome	Serum levels at enrollment (1975–1985)	This study did not find a significant difference in odds ratio of thyroid disease in people with elevated PBB exposure	This study did not use biological marker measurements for thyroid hormone markers	84
Diabetes						
18–28 y: health surveys administered in 1991 and 2001	1,384 Emory cohort adults (20 to >60 y of age)	Clinically defined outcome	Serum levels at enrollment (1975–1985)	There was no association between PBB serum levels and diabetes incidence	Available data made it difficult to distinguish between juvenile and adult diabetes diagnoses	85
Liver function						
12 y: data collected at MI clinics in 1985	51 MI farmers 20–79 y of age	Biological marker measurement	Serum levels at enrollment (1975–1985)	Cytochrome P450 markers were elevated in subjects exposed to PBB, suggesting reduced liver function	The study had a small sample size and unclear comparison group	86
Cancer						
5–20 y: baseline and follow-up surveys sent to the MDHHS cohort	20 cases, 290 controls from MDHHS cohort women matched on gender, race, and date of birth ±2 y (no ages provided)	Clinically defined outcome	Serum levels at enrollment (1975–1985)	Women with higher serum levels had a higher estimated risk of breast cancer	Small number of breast cancer cases. Study may not have had enough time since exposure to get a comprehensive picture of PBB exposure and associated cancers.	87
3–20 y: baseline and follow-up surveys sent to the MDHHS cohort	187 cancer cases, 696 controls from MDHHS cohort matched on sex and age (<19 to >70 y of age at enrollment)	Clinically defined outcome	Serum levels at enrollment (1975–1985)	Researchers observed an increasing dose-response relation between digestive cancers and serum PBB levels	The study had small cell sizes when stratifying by cancer types.	88
1–31 y: PBB cohort records were matched to the MI Cancer Registry from 1974 to 2004	51 cases, 202 age-matched controls from Emory cohort women (mean age at exposure = 42.7 y)	Clinically defined outcome	Serum levels at enrollment (1975–1985)	The odds ratio of having breast cancer among women with PBB concentrations 10 ng/mL compared with women with PBB concentrations at or below the limit of detection was 2.60	This study had a small sample size impacting the precision of the reported results	89
24 y: Questionnaire administered in 1997	951 Emory cohort women (age at exposure ≤8 to >51 y)	Clinically defined outcome	Serum levels at enrollment (1975–1985)	No association between serum PBB levels and benign breast disease	Information was not available to stratify reported breast disease by severity	90
24 y: Questionnaire administered in 1997	956 Emory cohort women (mean age at exposure = 22 y; age at interview = 24 to >50 y)	Clinically defined outcome	Serum levels at enrollment (1975–1985)	Did not see an association between PBB and abnormal Pap tests	Relied on self-reported abnormal Pap tests and only verified tests in that group	91

Table 4. (*Continued.*)

Time since exposure event (1973)	Sample size and population	How the outcome is measured	Assessment of exposure	Main findings (from researchers)	Comments	Citation
Endometriosis						
24 y: Questionnaire administered in 1997	943 MDHHS cohort women (mean age at exposure = 22 y; mean age at interview = 45 y)	Clinically defined outcome	Serum levels at enrollment (1975–1981)	No observed association between PBB exposure and endometriosis	This study had limited participants with the outcome (endometriosis)	92
Menstrual function						
24 y: Questionnaire administered in 1997	337 MDHHS cohort women (mean age at interview = 37.8 y)	Self-reported signs and symptoms	PBB levels estimated at the time of the survey	Among women with recent weight loss, PBB is associated with ovarian function, indicated by menstrual cycle and bleed length	Used self-reported menstrual cycle information	93
31–33 y: Survey administered 2004–2006	70 Emory cohort women (35 to 42 y of age at interview)	Biological marker measurement	Serum levels at enrollment (1975–1985)	Results are consistent with a hypothesized effect of exposure to an exogenous estrogen agonist	Small sample size due to stringent exclusion criteria	94
Time to menopause						
24 y: Questionnaire administered in 1997	990 MDHHS cohort women (mean age at interview = 36.2 y)	Self-reported signs and symptoms	Serum levels at enrollment (1975–1985)	No association between PBB exposure and time to menopause.	Included women using hormone replacement therapy, which could bias results	95
Pregnancy/birth outcomes						
39–42 y: Surveys conducted between 2012 and 2015	254 Emory cohort women (18.50–58.70 y of age at blood draw)	Self-reported signs and symptoms, Clinically defined outcome	Serum levels at time of survey/data collection (2012–2015)	These results show no association between PBB and the studied pregnancy outcomes or birth outcomes	Relied on self-reports for several outcomes	96
24 y: Questionnaire administered in 1997	861 MDHHS cohort women (mean age at interview = 39 y)	Self-reported signs and symptoms, clinically defined outcome	Serum levels at enrollment (1975–1985)	These results show no association between PBB exposure and risk of spontaneous abortion	Unable to include BMI due to data limitations	97
Immune function						
39–47 y: Surveys administered 2012–2020	674 F0 cohort members; 221 F1 cohort members (full sample mean age = 53 y)	Self-reported signs and symptoms	PBB levels measures from 2012–2020	PBB was not associated with a composite of any autoimmune disorder, but there was an unadjusted positive association between rheumatoid arthritis in males.	This study was limited by sample size, especially for analyses of specific conditions, and the potential for residual confounding	98
PBB biological marker measurement						
—	380 MDHHS cohort adults	Biological marker measurement	Serum levels at enrollment (1975–1985) and follow-up	Showed that calculated PBB elimination model can be used to estimate the body burden after exposure	PBB is dependent on the adiposity of the individual and could not be accounted for with available data	5
—	1974 Emory cohort participants	Biological marker measurement	Serum levels from 1974 to 2019	Refined elimination model using more recent serum samples and a larger sample size. Consistent with previous study showing that calculated PBB elimination models can be used to estimate PBB levels	Due to missing data, there could be issues of unmeasured confounding over time	58
Neurodevelopmental disorders						
—	44 F0 Emory cohort members exposed before age 10 y in 1973 (11 cases, 33 controls)	Self-reported signs and symptoms	Serum levels at time of survey/data collection (2012–2015, 2017–2019)	PBB was not associated with ADD/ADHD disorder in this analyses.	This study was limited by sample size, self-report of the outcome, and assessment of PBB levels decades after initial exposure	99

Note: —, no data; ADD/ADHD, attention-deficit disorder/attention-deficit hyperactivity disorder; BMI, body mass index; F0, first generation exposed through diet and occupation; F1, second generation exposed *in utero* and through breastfeeding; MDHHS, Michigan Department of Health and Human Services; MI, Michigan; PBB, polybrominated biphenyls; WI, Wisconsin.

Table 5. Summary of the effects of PBB exposure in the F1/F2 generations.

Health outcome	Association	Literature summary	Citations
Birth weight and gestational age	±	Studies found no association between PBB exposure and gestational age. There was a decreased birthweight in babies born to women or men with higher levels of PBB.	112, 113, 115
2D:4D digit ratio	+	Higher *in utero* PBB-153 exposure was associated with a more feminized digit ratio in F1 female participants, suggesting PBB's estrogenic effects, whereas no association was found in males.	117
Apgar scores	+	Among mothers exposed as children, higher maternal PBB was associated with lower Apgar scores at 1-minute.	118
Secondary sex ratio	+	The overall proportion of male offspring was higher in the PBB cohort than in the general population. There was also an increased odds of a male birth comparing the higher combined parental exposure to lower combined exposure.	119
Adverse reproductive outcomes	+	PBB exposure *in utero* was associated with increased self-reported adverse pregnancy outcomes, including spontaneous abortion.	114
Genitourinary conditions	+	Sons of highly-exposed women were more likely to report any genitourinary condition compared with those with least exposed mothers.	120
Female growth and development	+	Breastfed daughters of mothers with high PBB levels had earlier menarche compared with daughters of mothers with low PBB levels.	121, 122, 124
Male growth and development	+	Results suggest that sons of mothers with high PBB exposure levels have an increased likelihood of delayed puberty.	125
Immune function	±	In comparison with the lowest tertile, those in the highest tertile of PBB exposure were slightly more likely to report autoimmune disorders.	110
Neurodevelopmental outcomes	−	Odds ratios were null for higher PBB levels with ADD/ADHD (self-reported or mother-reported) and autism spectrum disorder (mother-reported).	111
Menstrual function	±	Comparing categories of *in utero* PBB, higher PBB was positively associated with progesterone metabolite levels in the luteal phase; other characteristics were null (follicular or luteal phase cycle length, average cycle length, bleed length, or creatinine-adjusted estrogen metabolite or follicular stimulating hormone levels).	126

Note: + indicates an association (any direction) between PBB and the outcome; ± indicates mixed results; − indicates null results. ADD/ADHD, attention-deficit disorder/attention-deficit hyperactivity disorder; F0, first generation exposed through diet and occupation; F1, second generation exposed *in utero* and through breastfeeding; PBB, polybrominated biphenyls.

losses) reported a higher prevalence of symptoms than residents of the respective farm groups from which these products came. It was further suggested that the disruption of communities following the contamination and uncertainty of health effects from PBB exposure may have exacerbated consumer symptoms.

Additional studies. Stross et al. studied the possible psychological effects of PBB exposure in a sample of 46 farmers from quarantined farms with incapacitating health complaints.[63] The participants in that study underwent a psychiatric evaluation and various psychological tests, including depression, IQ and memory tests, and neurological testing, including nerve conduction. The results of these tests were compared to population-based results rather than to a comparison group. No associations were found with PBB levels, though details on the statistical methods for these comparisons were not included.

A study (published in 1979) comparing performance tests of memory, motor strength and coordination, and cognitive functioning between 21 Michigan farm residents (mean age: 41.4 y) and 21 presumably unexposed hospital staff volunteers found no differences based on multivariate analysis of variance (MANOVA) tests.[68] The study authors suggested that group differences in the Minnesota Multiphasic Personality Inventory suggested more depressive symptoms among the Michigan farm residents. Proposed reasons for the observed difference between the farm residents and the hospital staff workers include the significant personal and financial loss and trauma related to the PBB contamination for affected farm families in comparison with hospital staff, or sampling variability, because this study had a much smaller sample size than the Mount Sinai analysis. An extension of this study (published in 1981) examining 25 Michigan chemical workers (mean age: 38.3 y) did not find a significant association between adipose PBB levels and scores on six memory tests.[54]

Thyroid Disease

Two studies conducted within 5 y of the contamination event assessed thyroid disease prevalence but did not compare rates by PBB level. The first, conducted in 1976 among participants 1–89 y of age, found a higher prevalence among participants from Michigan ($n = 399$, 8.5%) than those from Wisconsin ($n = 143$, 5.6%); however, the difference was not statistically significant based on chi-square tests.[46]

A separate study in 1978 compared rates of hypothyroidism (defined by thyroxine index) among chemical workers at the Velsicol Chemical Plant ($n = 35$; mean age: 35.9 y) and local men working in other occupations ($n = 89$; mean age: 37.5 y).[74] The prevalence of primary hypothyroidism was higher among the chemical workers than among the comparison group (11.4% vs. 0%), as was the prevalence of elevated serum thyrotropin concentration ($p = 0.006$). A final study in 1982 compared serum PBB levels to various clinical markers and found that thyroxine levels were inversely associated with PBB levels in both adults and children; however, these associations were not statistically significant.[59]

Diabetes

Mount Sinai studies. One study conducted 3 y after the contamination event compared diabetes prevalence between participants from Michigan ($n = 406$) and Wisconsin ($n = 153$) and found no difference (2.8% in each group) in unadjusted analyses.[46] Differences in diabetes prevalence were not examined by PBB level.

Additional studies. Landrigan et al. compared diabetes rates between quarantined farm residents ($n = 2{,}148$), farm product consumers ($n = 1{,}421$), chemical workers ($n = 251$), a control group with low PBB levels ($n = 57$), farmers with low PBB levels ($n = 331$), and self-referred volunteers with no direct connection to contaminated farms ($n = 337$) 1 y after the contamination

Table 6. Research on effects of PBB exposure on the second generation (F1) of Michigan residents.

Time since exposure event (1973)	Sample size and population	How the outcome is measured	Assessment of exposure	Main findings (from researchers)	Comments	Citation
Health outcome						
Reproductive outcomes						
24 y: Questionnaire administered in 1997	142 pregnancies from 73 daughters of exposed women in the Emory cohort (age 13–28 y at conception)	Clinically defined outcome	Mother's estimated PBB levels while child *in utero*	Infertility was not associated with PBB exposure *in utero*. There was a trend of increased odds of spontaneous abortions	Study was limited by number of women in the F1 generation wanting to be pregnant, leading to small sample size	100
2–30 y: Children born between 1975 and 2003	336 children of 155 men in the cohort (age not provided)	Birth records	Used maternal and paternal PBB levels at enrollment (1975–1985)	Observed dose–response associations across paternal PBB tertiles with offspring's lower birth weight. Paternal PBB was not associated with the risk of preterm birth.	Used enrollment PBB levels and did not adjust for time between exposure and offspring birth and small sample size in different birth outcomes may have contributed to null results	101
2–26 y: births between 1975–1997	899 infants born to 444 women in the MDHHS cohort (15–44 y of age at time of birth)	Birth records	Serum levels at enrollment (1975–1985)	No association was observed between PBB and gestational age. A negative association was observed between high PBB levels of enrollment serum samples and birth weight.	Used enrollment PBB levels and did not estimate PBB at time of gestation and is missing some potentially important covariates dues to data limitations	102
2–23 y: births between 1975–1994	1,111 infants born to 594 MDHHS cohort women (<10–42 y at exposure)	Self-reported signs and symptoms	Serum levels at enrollment (1975–1985)	Early age of exposure to PBB resulted in increased infant birth weight	The study did not model PBB exposure *in utero* and instead used PBB levels taken at baseline.	103
Growth and development						
24 y: Questionnaire administered in 1997	308 daughters of women in the MDHHS cohort (5–24 y of age)	Self-reported signs and symptoms	Mother's estimated PBB levels while child *in utero*	The study did not show an association between PBB exposure and growth and development.	This study used self-reported height/Weiwei.	104
24 y: Questionnaire administered in 1997	327 daughters of women in the MDHHS cohort (5– 24 y)	Self-reported signs and symptoms	Mother's estimated PBB levels while child *in utero*	Breastfed girls exposed to high estimated levels of PBB *in utero* had an earlier age at menarche.	The study was underpowered to perform stratified analyses on length of time breastfed.	105
30–33 y: Survey administered 2003–2006	809 sons of women in the MDHHS cohort (5–17 y of age)	Clinically defined outcome	Mother's estimated PBB levels while child *in utero*	Findings suggest sons exposed to PBB *in utero* are more likely to experience delayed puberty.	Puberty stage was self-reported.	106
Apgar scores						
5–32 y: Apgar scores from 1978 to 2005	613 infants from 330 women in the Emory cohort (<25 to 35 y of age)	Validated tests/scales (Apgar scores)	Mother's estimated PBB levels while child *in utero*	Maternal PBB exposure was associated with a dose-related increase in the odds of a below median Apgar score at 1 minute and 5.	Apgar scores were right-skewed, and there was not enough power to stratify in the lower scores.	107
Digit ratio						
39–41 y: Data collected between 2012 and 2014	F0 participants: 207 (82 males, 125 females; mean age for males = 49.83 y; mean age for females = 49.87 y) F1 participants: 51 (19 males 32 females; mean age for males = 30.45 y; mean age for females = 33.38 y)	Clinically defined outcome	Serum levels at time of survey/ data collection	An association was found between prenatal levels of PBB and the digit ratio in adult women.	Included a small number of participants born after exposure (F1), but not powered to complete analysis	108
Genitourinary (GU) conditions						
30–33 y: Survey administered 2003–2006	809 sons of women in the MDHHS cohort (5–17 y of age)	Clinically defined outcome	Mother's estimated PBB levels while child *in utero*	Sons of women highly exposed to PBB are more likely to report any genitourinary condition.	Genitourinary conditions were self-reported.	106

Table 6. (*Continued.*)

Time since exposure event (1973)	Sample size and population	How the outcome is measured	Assessment of exposure	Main findings (from researchers)	Comments	Citation
Secondary sex ratio						
1–15 y: Birth records between 1975–1988	865 infants born to 479 cohort adults (mother's mean age at exposure = 17 y; father's mean age at exposure = 25 y)	Birth records	Serum levels at time of data collection	In this population, combined parental exposure to PBBs increased the odds of a male birth.	Exposure status was not available for both parents for all recorded births	109
Immune function						
39–47 y: Surveys administered 2012–2020	674 F0 cohort members; 221 F1 cohort members (full sample mean age = 53 y)	Self-reported signs and symptoms	PBB levels measures from 2012 to 2020	In adjusted models, there was no significant association between PBB-153 levels and self-reported autoimmune disorders.	Limited sample size and young population in the F1 sample may have limited the power of the analysis.	98
Other						
PBB transfer to F1	145 mother–child pairs from the MDHHS cohort	Biological marker measurement	Serum levels at time of survey/ data collection	Among mothers with a detectable serum PBB concentration, those who breastfed more than 5.5 months were 6 times more likely to have a child with a detectable serum PBB concentration, in comparison with a non-breast-fed child.	F1 PBB serum levels were collected at different times during childhood.	55
Neurodevelopmental disorders						
39–46 y: Surveys administered 2012–2019	F1 Emory cohort members: 35 cases and 105 controls in the self-reported ADHD analysis; 38 cases and 56 controls in the mother-reported ADHD analysis; 13 cases and 30 controls in the mother-reported ASD analysis	Self-reported or mother-reported signs and symptoms	Serum levels at time of survey/ data collection (2012–2015, 2017–2019)	PBB was not associated with ADHD or ASD in this analyses.	This study was limited by sample size, self-report of the outcome, and use of mother's contemporary PBB levels as a proxy for the F1 subject's *in utero* exposure.	99
Menstrual function						
—	41 daughters of women in the Michigan PBB Registry	Biological marker measurement, self-reported signs and symptoms	Mother's estimated PBB levels while child was *in utero*	Higher estimated *in utero* PBB exposure was associated with increased progesterone levels during the luteal phase. Most other menstrual cycle characteristics were not associated with *in utero* PBB exposure.	Limited by small sample size	110

Note: —, no data; ADD/ADHD, attention-deficit disorder/attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; BMI, body mass index; F0, first generation exposed through diet and occupation; F1, second generation exposed *in utero* and through breastfeeding; MDHHS, Michigan Department of Health and Human Services; PBB, polybrominated biphenyl.

Table 7. Summary of research on epigenetic and metabolomic effects of PBB exposure.

Health outcome	Association	Literature summary	Citations
Genome-wide DNA methylation differences	+	1890 CpG sites were associated with PBB exposure, including CpGs associated with estrogen. A further study found that the CpG sites affected may be sex-specific. PBB exposure was also associated with increased SEMs and biological age acceleration.	127–129, 134
Metabolomic variations	+	There were associations in metabolomic pathways related to neurodegenerative diseases. It was also noted that different pathways were impacted across different generations (F0 or F1).	45, 138
Spermatogenic epigenome	+	PBB impacted the epigenome of spermatogenic cells, offering a potential explanation for health effects observed among children of exposed men.	133

Note: + indicates an association (any direction) between PBB and the outcome. F0, first generation exposed through diet and occupation; F1, second generation exposed *in utero* and through breastfeeding; PBB, polybrominated biphenyl; SEM, stochastic epigenetic mutations.

event.[42] Diabetes prevalence did not differ significantly between groups in unadjusted analyses.

Cancer

Mount Sinai studies. In a study conducted in 1976, the prevalence of elevated carcinoembryonic antigen (CEA) plasma levels (>2.5 ng/mL), a nonspecific marker of cell changes primarily used to screen for malignant and nonmalignant gastrointestinal tract tumors, was higher but not statistically significantly different between Michigan ($n = 611$, 12.3%) and Wisconsin ($n = 138$, 6.5%) dairy farmers based on chi-square test.[75] Within the Michigan sample, however, the prevalence of elevated CEA was significantly greater among smokers with serum PBB levels ≥10 ppb ($n = 17$) in comparison with smokers with <10 ppb ($n = 83$).

Additional studies. Landrigan et al. compared incidence rates of self-reported cancer from 1973 to 1977 among six groups of Michigan residents (quarantined farm residents, $n = 2{,}148$; consumers, $n = 1{,}421$; chemical workers, $n = 251$; nonfarmers with low PBB levels, $n = 57$; farmers with low PBB levels, $n = 331$; and volunteers, $n = 337$).[42] The incidence of any cancer was 0% among participants with nondetectable PBB levels ($n = 89$) and 1.8% among participants with PBB >100 ppb ($n = 126$) (no statistical test was provided).

Mortality

A study (published in 1984) led by a scientist affiliated with the Velsicol Chemical Company examined causes of death in 3,579 workers employed between 1935 and 1976 at three manufacturing plants (two in Michigan and one in Arkansas).[76] Participants were grouped by job category into those who were "routinely" exposed to a chemical (production, quality control, and shipping) and those who were "nonroutinely" exposed (research, maintenance, and transportation). None of the 91 men potentially with "routine" PBB exposure died during the study period. The researchers found two deaths among 237 men who may have had nonroutine PBB exposure, in comparison with 6.36 expected. This study may have ended too soon following exposure to determine whether PBB increased premature mortality risk. The lower number of deaths observed than expected among those potentially exposed to PBB may have resulted from healthy worker bias.

Birth Outcomes

An ecological study examined secular trends in Michigan's fetal mortality from 1966 to 1981, defined as death at >20 wk gestation.[77] The comparison was based on fetal deaths per live births in Michigan counties, with two levels of exposure based on the proportion of quarantined farms per county (>5% vs. ≤5%). Preexposure years were defined as 1966–1973, and postexposure years were defined as 1974–1981. There was no difference in infant mortality after exposure when comparing counties with and without a high proportion of quarantined farms.

Effects on Participants Exposed in Infancy through Adolescence

Acute and subacute effects of PBB exposure were studied in 1976 among Michigan residents who ate contaminated food as children (0–16 y of age). A preliminary study compared the prevalence of ∼65 symptoms (broadly including dermatological, neurological, and gastrointestinal issues) reported by Michigan children ($n = 443$) to those reported by Wisconsin children ($n = 72$).[79] Overall, the prevalence of all but one symptom (allergic disorders) was higher in Michigan than in Wisconsin children. Children from quarantined farms did not have a higher prevalence of multiple symptoms than those from nonquarantined farms.

A more detailed follow-up study of symptoms reported by parents in 1976 in the same sample of children (age 0–16 y) measured PBB levels rather than using residency as a proxy for PBB exposure.[80] For 32 of 59 symptoms assessed, mean PBB levels were statistically significantly lower among the children with the symptom than among those without the symptom, based on unadjusted *t*-tests. For three symptoms (pneumonia, urinary tract infection, and bedwetting), mean PBB levels were higher in comparison with those without the symptom, based on unadjusted *t*-tests. Further, it was reported that the children with the highest serum PBB concentrations were younger in comparison with children with lower serum PBB concentrations. The child with the highest PBB level (1,625 ppb, $n = 10$ ppb) had a PBB measurement an order of magnitude higher than the next highest and was classified as an extreme outlier and excluded from the analyses. The analysis did not account for clustering by family.

Another study compared growth, development, motor skills, and prevalence of infections and other symptoms among exposed ($n = 33$ from quarantined farms) and unexposed children ($n = 20$ from other areas) born from 1973 to 1975 and evaluated in 1977.[73] These children were exposed to PBB *in utero* and/or early childhood. This study found no differences between exposed and unexposed children for any studied outcome, including an assessment by a pediatric neurologist. In a follow-up study in the same sample, researchers tested 19 young children's neurological ability in association with PBB measured in adipose tissue, all exposed *in utero* and/or in infancy.[70] The results showed lower scores on all five neurobehavioral tests with higher PBB adipose concentration, both when PBB was treated as a continuous variable in Pearson's correlation analyses (correlation coefficients ranged from −0.30 to −0.52, $p < 0.05$ for four of five tests), and when dichotomized at the median in MANOVA tests controlling for parental education (high

Table 8. Epigenetic and metabolomic research describing biological mechanisms and pathways PBB could interact with to cause adverse health effects.

Time since exposure event (1973)	Sample size and population	Methods	Main findings	Comments	Studies
31–42 y: Blood samples collected between 2004 and 2015	658 Emory cohort adults (mean age = 54.3 ± 12.7 y; mean age at exposure 15.2 ± 11.5 y)	Analyzed peripheral blood samples for differences in DNA methylation associated with PBB exposure	Observed differences in epigenetic marks suggest PBB is acting similarly to estrogen and is associated with dysregulated immune system pathways.	Smoking and BMI were unable to be considered due to lack of available data.	111
31–42 y: Blood samples collected between 2004 and 2015	658 Emory cohort adults (mean age = 54.3 ± 12.7 y; mean age at exposure 15.2 ± 11.5 y)	PBB association with SEMs were tested in serum samples	Findings showed an association between PBB serum levels and increased SEMs, especially in those exposed as older adults.	Due to small cell sizes when stratified, researchers were unable to link to specific outcomes.	112
31–42 y: Blood samples collected between 2004 and 2015	658 Emory cohort adults (mean age = 54.3 ± 12.7 y; mean age at exposure 15.2 ± 11.5 y)	PBB exposure and accelerated biological aging	When stratified, men exposed before finishing puberty had an association between PBB and accelerated aging.	This observed association might be due to unmeasured confounding from other biological mechanisms.	113
31–42 y: Blood samples collected between 2004 and 2015	381 women (mean age = 51.2 ± 12.4 y; mean age at exposure 12.7 ± 10.7 y); 277 men (mean age = 58.6 ± 12.0 y; mean age at exposure 18.5 ± 11.8 y)	Looked at sex-specific DNA methylation differences associated with PBB exposure	PBBs were associated with sex-specific methylation differences in the epigenome, which may underlie sex-specific health outcomes.	Underpowered to look at methylation sites that explained <8% of the variance.	114
31–42 y: Blood samples collected between 2004 and 2015	65 cases (mean age = 48.9 ± 9.2 y) and 240 controls (mean age = 50.0 ± 11.5 y) from Emory cohort adult women	Looked at DNA methylation and the association with endometriosis and whether this relationship was dependent on PBB levels	After correcting for multiple testing, no methylated sites remained significant	Data on menstrual cycle phase was not available to researchers.	115
39–41 y: Data collected between 2012 and 2014	Emory cohort adult men (no age provided)	Investigated the effects of PBB on epigenetic regulation in sperm	Results suggest that PBB exposure alters the epigenome by disrupting methyltransferase activity.	Unclear how many biological samples were analyzed, and study was limited by a small sample size.	116
38–41 y: Serum samples collected between 2011 and 2014	156 Emory cohort adults (mean age = 39.7 ± 11.0 y)	Conducted an untargeted, metabolic profiling of plasma and feature association with PBB exposure	The results from this study showed that metabolic alterations correlated with PBB exposure can be detected in human populations.	Limited to known metabolites listed in databases and did not try to uncover any novel metabolite associated with PBB exposure.	45
40–41 y: Serum samples collected between 2013 and 2014	498 Emory cohort adults (mean age = 51.5 ± 17.1 y)	Conducted an untargeted metabolomic-wide association study with biological pathway analysis and feature annotation	The results from this study were in line with previous research and demonstrated that PBB can cause biological perturbations.	Limited to known metabolites listed in databases and did not try to uncover any novel metabolite associated with PBB exposure.	117

Note: BMI, body mass index; DNA, Deoxyribonucleic acid; F0, first generation exposed through diet and occupation; F1, second generation exposed *in utero* and through breastfeeding; MDHHS, Michigan Department of Health and Human Services; MI, Michigan; PBB, polybrominated biphenyl; SEM, stochastic epigenetic mutations.

exposure group: >100 ppb, $n=10$, range 116–20,960 ppb; low exposure group: <100 ppb, $n=8$, range 10–74 ppb; $p<0.05$ for four of five tests).

In another follow-up of 18 of the same 19 children, by then 4–6 y of age, researchers found no difference in development and intelligence tests by low or high exposure.[69] In most areas assessed, the children scored higher than the standardized means on the tests. However, a negative association was found between natural log-transformed continuous PBB exposure and performance scores on perceptual tasks (Pearson $r=-0.51$, $p<0.01$).

Long-Term Effects in the F0 Generation: Findings from Later Studies (Published 1990–2023)

Thyroid function. Yard et al. conducted a nested case–control study within the PBB registry to study the association of PBB exposure with a cumulative incidence of self-reported thyroid dysfunction 24 y following exposure.[84] Exposed participants ($n=3,333$), free of thyroid disease in 1974, were asked about incident thyroid dysfunction. Incidence was 13.9% among women ($n=212$ cases) and 2.6% among men ($n=47$ cases). The odds of thyroid dysfunction did not differ by PBB level [adjusted odds ratio (OR) comparing highest to lowest PBB serum level = 0.76; 95% confidence interval (CI): 0.47, 1.24].

A cross-sectional study of adults from the Michigan PBB Registry assessed 31–33 y after exposure examined associations of PBBs and PCBs with thyroid disease ($n=753$, including 105 cases) and thyroid hormone levels ($n=551$).[83] Among women, the OR for any thyroid disease was 1.12 (95% CI: 0.83, 1.52; $n=105$ cases), and for hypothyroidism was 1.35 (95% CI: 0.86, 2.13; $n=49$ cases) per interquartile increase in PBB-153 (0.43 ng/mL). Among men, the odds ratio for any thyroid disease per interquartile increase in natural log-transformed PBB-153 (0.76 ng/mL) was 0.69 (95% CI: 0.33, 1.44; $n=21$ cases).

A cross-sectional study using serum samples collected between 2004 and 2015 examined associations between thyroid hormone levels and PBBs in 715 adults (mean age: 51 y) exposed as children. This study found that PBB exposure was associated with thyroid hormone measures (negatively associated with free thyroxine and positively associate with total and free triiodothyronine as well as the ratio of free triiodothyronine to free thyroxine) and that this relationship was only evident among participants exposed at ≤16 y of age.[82]

These more recent findings contrast with more mixed results of older PBB studies but are consistent with studies on structurally similar PCBs[121,122] and PBDEs.[123–126] These discrepant findings may be related to the longer follow-up period of more recent studies, allowing more time for the disease to manifest, as well as to improved exposure assessment, outcome assessment, and statistical methodologies. Jacobson et al. also included individuals exposed at younger ages who, on average, experienced worse health outcomes associated with PBB.[69] Reinforcing the critical influence of age at exposure on health outcomes, Curtis et al. found a stronger association among those exposed ≤16 y of age.[82]

Diabetes. Vasiliu et al. conducted a retrospective cohort study (between 1991 and 2001) among members of the original Michigan Long-Term PBB study to evaluate the association between PBB exposure and risk of developing Type II diabetes.[85] Diabetes rates did not differ by PBB level in males or females (rates in highest vs. lowest PBB-exposed groups: 12% vs. 12% among males, 11% vs. 14% among females).

Liver. Liver function was assessed in 1985 using the caffeine breath test (CBT) and caffeine urinary metabolite ratio (CMR), which indirectly assessed P-450 enzyme activity. This study found that those with PBB exposure had reduced liver enzyme activity compared with an unexposed group from Chicago and Toronto originally recruited for a separate study.[86]

Cancer. An earlier[87] and more recent[89] nested case–control study of breast cancer in the Michigan PBB Registry found a positive association between PBB and breast cancer development. The earlier study matched 20 breast cancer cases diagnosed from 1978 to 1993 to 290 controls and found an increased risk (adjusted OR = 3.3; 95% CI: 0.9, 11.4) associated with PBB levels ≥2 ppb in comparison with those <2 ppb.[85] The more recent study included 51 cases diagnosed from 1974 to 2004, age-matched to 202 controls, and found dose-related elevated ORs for invasive breast cancer for women by PBB quartile. Those in the highest quartile (≥10 ng/mL) were at increased risk in comparison with those in the lowest quartile (≤1 ng/mL, LOD; OR = 2.60; 95% CI: 0.93, 7.27).[89]

Hoque et al. conducted a case–control study within the PBB registry for several cancer sites, with 187 cases diagnosed from 1974 to 1993 matched to 696 controls.[88] Although no association was found between PBB level and all-site cancer risk, a dose–response association was found for digestive system cancers (liver, stomach, esophagus, and pancreas; $n=12$ cases) and lymphoma ($n=8$) across four PBB exposure levels (≤3, >3–20, >20–50, >50 ppb). These findings were based on small numbers of cases, yielding very wide CIs and likely inflated ORs due to sparse data bias.[127] An elevated odds for breast cancer ($n=25$ cases) was found only for the >3–20 ppb group in comparison with the lowest PBB-level group (adjusted OR = 2.41; 95% CI: 0.92, 6.30).

A 1997 study of 956 women in the PBB registry found a slightly elevated, though not statistically significant, risk of self-reporting an abnormal Pap test result (a risk for cervical cancer) among highly exposed women (≥90th percentile, PBB ≥13 μg/L) in comparison with women with nondetectable PBB concentrations [hazard ratio (HR) = 1.23; 95% CI: 0.74, 2.06].[91]

The incidence of self-reported physician-diagnosed benign breast disease was studied in a retrospective cohort study of 951 women from the PBB cohort assessed through 1997.[90] No significant association was found for exposure to moderate (1–12 ppb, adjusted HR = 1.08; 95% CI: 0.80, 1.45) or high (>12 ppb, HR = 0.79; 95% CI: 0.46, 1.38) levels of serum PBB in comparison with levels <1 ppb.

Endometriosis, menstrual function, and time to menopause. In a study conducted in 1997 among 943 reproductive-age women from the PBB registry, 79 (9%) reported having endometriosis.[92] Survival analysis was used to evaluate the time to develop endometriosis by PBB level at enrollment. No relationship was observed (HR = 1.01; 95% CI: 0.60, 1.69 for PBB >4 ppb in comparison with ≤1 ppb).

From a 1997 survey, F0 women not using oral contraceptives or other hormonal medications were included in an analysis of self-reported menstrual cycle characteristics ($n=337$).[93] No overall association was found between menstrual cycle characteristics and PBB tertiles based on estimated levels at the time of the study (PBB tertiles defined as <0.06, 0.06–0.32, and >0.32 ppb). However, researchers found a significant interaction between PBB exposure and weight loss, possibly related to mobilization of PBB from fat stores into the blood stream following weight loss.[128,129] Longer bleed length and shorter cycle lengths were associated with higher PBB exposure among women who lost more than 10% of their body weight in the past year. Although this finding might suggest that PBB mobilization from lipid stores is important, it could also result from exposure mismeasurement for women with recent weight loss, because the elimination model used to estimate current PBB levels included BMI as a predictor.

A subsequent study (conducted 2004–2006), incorporating daily urine samples for measurement of hormone metabolites and menstrual function in 70 women exposed to PBB via diet before menarche, found that categorized PBB levels >3.0 and >1–3.0 ppb were associated with lower estrone 3-glucuronide (E1-3G) levels across the menstrual cycle and lower FSH levels during the follicular phase, in comparison with PBB levels ≤1.0 ppb.[94]

Blanck et al. analyzed a 1997 survey that included self-reported age at menopause and symptoms among 874 women 24–79 y of age in the PBB cohort.[95] A survival analysis beginning at the time of exposure found no association between PBB and time to menopause. The adjusted survival ratios were 0.92 (95% CI: 0.72, 1.17) for >1–13 ppb vs. ≤1 ppb and 0.78 (95% CI: 0.50, 1.20) for ≥13 ppb vs. ≤1 ppb.

Pregnancy outcomes. Small et al. studied the possible association between maternal PBB exposure and spontaneous abortion (pregnancy ending before 20 gestational weeks) from a 1997 survey.[97] Exposure was defined as serum PBB level at the time of conception (estimated using an elimination model) and categorized as <1, 1–2.9, and >2.9 ppb. The study population included 1,344 pregnancies among 529 women. Among mothers with PBB levels >2.9 ppb, the risk for spontaneous abortion was not significantly different than the risk among mothers with PBB below the LOD (adjusted OR = 0.73; 95% CI: 0.47, 1.13).

A 2020 cross-sectional study of reproductive health outcomes among 254 PBB-exposed women with data from 2012 to 2015 did not find any associations between PBB and several pregnancy and offspring outcomes, including the number of pregnancies, miscarriages, hypertensive pregnancy disorders, and gestational diabetes, as well as birth weight, gestational age, and birth defects among their F1 offspring.[96]

Immune function. A 2023 cross-sectional study examined associations between self-reported autoimmune disorders and serum PBB-153 levels measured in 2012–2020 among 674 F0 and 221 F1 individuals. PBB levels were not associated with a composite classification of any autoimmune disorders. However, among males, there was an unadjusted positive association between serum PBB levels and rheumatoid arthritis. Among females, there was an unadjusted positive association between serum PBB levels and rheumatoid arthritis, neurological autoimmune disorders, and thyroid autoimmune disorders; these associations were not statistically significant. There was also an unadjusted negative association between serum PBB levels and psoriasis among females. This study was limited by sample size, especially for analyses of specific conditions, and the potential for residual confounding.[98]

Neurodevelopmental outcomes. Christensen et al.[99] examined associations between adult serum PBB levels and self-reported attention-deficit/hyperactivity disorder (ADHD; 11 cases and 33 controls) among F0 participants exposed to PBB in childhood before age 10 y. They reported an elevated though not statistically significant OR (1.42; 95% CI: 0.51, 3.92) for PBB modeled as a continuous variable.

Effects in the F1/F2 Generations

Reproductive outcomes. Givens et al. studied the association between estimated PBB level at conception and gestational age and birth weight at delivery from 1975 to 1997 (889 infants of 444 mothers).[102] The study found no difference in gestational age or birth weight by maternal PBB at conception but did find lower birth weights among those with PBB levels >3.0 ppb at enrollment in comparison with those ≤LOD of 1 ppb (β = −98.84 g; 95% CI: −197.01, −0.68).

Redmond et al. examined associations between paternal enrollment PBB levels and birth outcomes among 336 offspring (born 1975–2003) of 155 men.[101] They observed dose–response associations across PBB tertiles with lower birth weight, with adjusted risk ratios of 1.67 (95% CI: 0.93, 2.99) and 2.06 (95% CI: 1.12, 3.79) for offspring in the lowest birth weight quartile for the middle and highest PBB tertiles, respectively, in comparison with the lowest tertile. Paternal PBB was not associated with the risk of preterm birth.

Small et al. examined whether *in utero* PBB exposure among 73 F1 daughters of F0 women was associated with self-reported adverse pregnancy outcomes when the F1 women reached adulthood from a 1997 survey ($n = 142$ pregnancies).[100] Among the most highly exposed women (≥3.17 ppb; $n = 66$), 26% of pregnancies ended in spontaneous abortion, in comparison with only 9% among those least exposed (≤1 ppb; $n = 62$), p for trend = 0.04. A significant dose–response relationship was observed between F0 mother's enrollment PBB level and their F1 daughter's risk of spontaneous abortion (p-trend = 0.05). No association was found between PBB levels and other reproductive outcomes, including time to pregnancy and infertility. Pregnancy-induced hypertension was less common in women with the highest estimated *in utero* PBB exposure, but there was no dose–response relationship. The relatively small sample in these analyses may have precluded the detection of some associations due to imprecision and precluded examination of other pregnancy complications.

Sweeney and Symanski studied the effect of maternal PBB level and age at exposure estimated by age at enrollment [≤10 (prepubertal), 11–16 (pubertal), and ≥17 y of age (postpubertal)] on pregnancy outcomes among births between 1975 and 1994.[103] The study included 1,111 births to 560 women in the PBB cohort, with birth certificates used to ascertain their infants' birth weights and gestational ages. No significant association was found between maternal serum PBB at enrollment and infant gestational age or birth weight in the total sample. When stratified by age at exposure, the authors reported associations (β′s from linear regression models) between mother's age at exposure and child's birth weight [linear regression β = 224.8 g ($p = 0.0116$) for mothers who had been ≤10 y of age at enrollment], between age at exposure and enrollment PBB level (inverse; descriptive only, no statistical test), and between enrollment PBB level and birth weight [linear regression β = 1.652 g ($p = 0.0043$)] but did not directly test for effect modification by age at exposure in the PBB–birth weight relationship. In this stratified sample, there was no association between maternal age or PBB level and gestational age at delivery. A published commentary and replication analysis noted methodological concerns with this study, including the inclusion of highly collinear model covariates (maternal age at enrollment, time from enrollment to infant's birth, and maternal age at infant's birth) that may have produced a spurious association between maternal exposure age and birth weight.[130]

Other birth outcomes. A 2016 study examined PBB exposure in relation to the 2D:4D digit ratio, a sexually dimorphic measure influenced by the *in utero* hormonal environment, among 258 individuals from the Michigan cohort.[108] Participants included 207 F0 individuals born before exposure (125 females, 82 males), and 51 F1 individuals born after February 1974 (32 females, 19 males). No association was found between concurrent PBB-153 levels and digit ratio. However, among 51 participants with estimated *in utero* PBB exposure, higher exposure (above the lowest tertile) was linked to a higher digit ratio in females (β = 0.393, $p = 0.062$ and β = 0.364, $p = 0.082$ for the second and third tertiles, respectively; p for trend = 0.11). Similar results were observed when dichotomized at the median, with no association found in males.

A study of infant Apgar scores in 613 infants born from 1978 to 2005 to 330 women in the Michigan PBB Registry found a dose–response increase in the odds of a below-median Apgar score at 1 and 5 min after birth with higher maternal PBB levels.[107] When stratifying by whether the mother was exposed at <9 or ≥9 y of age, they found higher odds of low 1-min Apgar scores for infants of mothers with PBB levels >1 ppb and who were exposed before age 9 y (>1 to <2.5 ppb, OR = 3.03, 95% CI: 1.29, 7.08; ≥2.5 ppb, OR = 3.54, 95% CI: 1.48, 8.47), but not for infants of mothers exposed ≥9 y of age.

One study examined the sex ratio among F1 offspring (born 1975–1988) of F0 parents. Of 865 in-state births (1975–1988) to mothers in the Michigan PBB Registry, there were 300 infants whose mother and father were both in the cohort.[109] The overall proportion of male offspring was 0.542, higher than the national male proportion of 0.514 (binomial test: $p = 0.10$). When both parents were in the cohort, the OR for male birth with higher combined maternal and paternal enrollment PBB exposure in comparison with low combined PBB exposure was 2.56 (95% CI: 1.32, 4.98). This OR was slightly attenuated for combined parents' PBB exposure at conception, estimated using an elimination model (adjusted OR = 2.47; 95% CI: 1.15, 5.28).

Genitourinary conditions. Maternal serum PBB at enrollment and estimated maternal PBB at conception were examined in relation to genitourinary conditions, including cryptorchidism and hypospadias, among males exposed to maternal PBB body burdens *in utero* whose mothers were exposed to PBB in 1973–1974.[131] In a survey administered between 2003 and 2006, sons (age 5–31 y) of highly exposed women (>5 ppb) were more likely to report any genitourinary condition in comparison with the least exposed (≤1 ppb) (OR = 2.0; 95% CI: 0.8, 5.1). This risk was increased when excluding sons born after the contamination but before the mother's serum PBB measurement (OR = 3.1; 95% CI: 1.0, 9.1). There was evidence of three times more reports of hernia or hydrocele among sons born to mothers with >5 ppb PBB exposure at enrollment in comparison with those with ≤1 ppb (test for trend $p = 0.04$).

Female growth, pubertal development, and menstrual function. Blanck et al. studied growth patterns reported in 1997 among 308 girls (mean age: 15.2 y, range: 5–24 y) exposed to PBB *in utero* or during early infancy.[104] No association was found between estimated perinatal PBB exposure and height or height adjusted for weight.

Blanck et al. also studied pubertal development and age at menarche from a 1997 survey of 327 girls with perinatal PBB exposure.[105] A total of 59.5% of the daughters were also exposed postnatally through breastfeeding. The researchers found an interaction between PBB level and breastfeeding such that breastfed daughters of mothers with high estimated serum PBB level at the time of pregnancy had earlier menarche (age 11.6 y) than daughters who had not been breastfed by mothers with low PBB (age 12.7 y).

Age at menarche has a large genetic component, and previous estimates of heritability averaged about 50%.[132] An estimation of the proportion of variance due to genetic factors for self-reported age at menarche and menstrual cycle length in this PBB-exposed population was calculated for 1,033 women (373 families).[133] Overall, heritability of at menarche was ∼50% (heritability, h2 = 0.53 ± 0.05); menstrual cycle length heritability was 0.42 ± 0.10. However, heritability of age at menarche varied by PBB exposure and was highest in those with low exposure (PBB <1 ppb, h2 = 0.61 ± 0.08), lower in the moderately exposed (PBB 1–3 ppb, 0.45 ± 0.16), and lowest in the highly exposed (PBB >3 ppb, 0.40 ± 0.16). The same trend was observed for menstrual cycle length.

Barat et al.[106] examined associations between estimated *in utero* PBB exposure levels and adult menstrual function among 41 reproductive-age F1 women born to F0 mothers exposed to PBB during the 1973–1974 contamination crisis. Higher estimated *in utero* PBB exposures were associated with higher progesterone metabolite (pregnanediol 3-glucuronide) levels across the luteal phase; other menstrual cycle characteristics [creatinine-adjusted E1-3G (an estrogen metabolite) or FSH levels, bleed length, average cycle length, and follicular or luteal phase cycle length] were not associated with estimated *in utero* PBB exposure levels.

Male growth and pubertal development. A survey administered from 2003 to 2006 collected information on development in boys exposed to PBB *in utero*.[110] A mailed questionnaire reported Tanner stage and current height and weight for sons 5–17 y of age. Sons 18–30 y of age were interviewed by telephone regarding current height and weight and recalled growth and development. Among sons 5–17 y of age, those with the highest exposure (>3 ppb) were less likely to report an advanced Tanner stage for genital development (OR = 0.4; 95% CI: 0.2, 0.9) or pubic hair development (OR = 0.5; 95% CI: 0.2, 1.0) in comparison with those with the lowest exposure (≤1 ppb) after adjusting for the current age. No differences were seen in growth among sons 5–17 y of age. However, among sons 18–30 y of age, those with higher exposure were more likely to weigh less and have lower BMI as adults (p-trend = 0.01 and 0.04, respectively). They were less likely to recall being tall (OR = 0.5; 95% CI: 0.2, 0.9) or heavy (OR = 0.6; 95% CI: 0.3, 1.1) in comparison with their peers at age 11 y.

Immune function. A cross-sectional study examining associations between self-reported autoimmune disorders and serum PBB-153 levels measured in 2012–2020 among both 674 F0 individuals and 221 F1 individuals did not find a significant association in either sex in adjusted models. It is possible that those exposed *in utero* may not have been old enough for autoimmune disorders to present [mean age = 31 y, interquartile range (IQR) = 12 y; all participants <46 y of age], limiting the ability to detect a significant trend.[98]

Neurodevelopmental outcomes. Christensen et al.[99] examined associations between serum PBB levels and self-reported attention-deficit/hyperactivity disorder (ADHD; 35 cases and 105 controls; respondents' PBB measured in 2012–2019), maternally reported ADHD (38 cases, 56 controls; mothers' PBB measured in 2012–2019), and maternally reported autism spectrum disorder (ASD; 13 cases, 30 controls; mothers' PBB measured in 2012–2019) among F1 participants. All three sets of case–control analyses produced null results [self-reported ADHD OR = 1.05 (95% CI: 0.79, 1.41); mother-reported ADHD OR = 0.87 (95% CI: 0.61, 1.25); mother-reported ASD OR = 0.46 (95% CI: 0.09, 2.32)] for PBB modeled as a continuous variable.

Epigenetics and Metabolomics: Evidence for Possible Biological Mechanisms of PBBs' Health Impacts

Several recent studies have used emerging technologies in epigenetics and metabolomics to elucidate biological mechanisms and pathways by which PBBs might induce adverse health impacts (Tables 7 and 8). These were conducted with a cross-sectional sample of 658 members of the Michigan PBB Registry [$n = 381$ women (age at time of study, mean = 51.2 ± 12.4 y; age at exposure, mean = 12.7 ± 10.7 y); $n = 277$ men (age at time of study, mean = 58.6 ± 12.0 y; age at exposure, mean = 18.5 ± 11.8 y)]. These studies used more recently measured (2003–2020) serum levels of PBB-153, the predominant congener in the commercial flame-retardant mixtures produced through the 1970s, with a lower LOD than the lab methods used in the 1970s–1990s. We summarize these findings separately from earlier "Results" sections above because they focus on biomarkers of mechanistic pathways rather than specific health outcomes, and the analyses

were conducted within a sample comprising both F0 and F1 individuals; results were not reported separately by generation.

DNA methylation differences. **Global DNA methylation.** Curtis et al. investigated genome-wide DNA methylation differences in peripheral blood by PBB blood level.[111] This study found 1,890 CpGs associated with PBB after multiple test corrections, with significant overlap with CpGs associated with estrogen and enrichment for pathways related to immune function and endocrine-mediated autoimmune disease.

Sex-specific DNA methylation. A follow-up analysis of sex-specific DNA methylation differences found that PBB levels associated with 675 CpGs in men but only 17 CpGs in women.[114] These CpGs were sex-specific and were enriched in different functional regions and binding sites in each sex; the authors suggested that PBB exposure may have sex-specific epigenetic effects.

SEMs. Another analysis by Curtis et al. examined stochastic epigenetic mutations (SEMs), which are DNA methylation values at particular sites that appear extreme in comparison with the rest of the study population.[112] SEMs have been linked to biological aging[134] and cancer progress.[135] They found that the association between PBB and SEM count was significant for those exposed at ages older than 13 y; they did not find differences by sex. SEMs were enriched in biological pathways related to endocrine function and xenobiotic metabolism.

Methylation by endometriosis status. A cross-sectional analysis by Gerkowicz, et al. of 305 women ($n=65$ cases, mean age: 48.9 y; $n=240$ controls, mean age: 50.0 y) in the Michigan PBB Registry examined DNA methylation differences in women with and without self-reported physician-diagnosed endometriosis.[115] They noted that cases had slightly higher PBB levels than controls (0.43 ng/mL vs. 0.30 ng/mL, $p=0.08$), though their finding of no association between PBB and endometriosis were consistent with Hoffman et al.[92] They found >39,000 CpGs associated with endometriosis, with enrichment for 68 biological pathways related to endocrine, oncological, immunological, and cell regulation processes; however, none remained significant after adjusting for multiple comparisons.

Methylation in sperm cells. A study published in 2020 using epidemiological and *in vitro* methods found that PBB-153 exposure was associated with hypomethylation in spermatogenic cells, offering a potential explanation for health effects observed among children of exposed men.[116] This study examined methylation patterns at four imprinted genes in sperm from 87 exposed Michigan PBB Registry members, 6 unexposed (not detectable) cohort members, and 6 sperm bank external controls and concluded that PBB exposure disrupted methyltransferase activity and altered the expression of critical genes in sperm development.

Age acceleration. Another analysis examined associations between PBB levels and three metrics of epigenetic age acceleration (intrinsic, extrinsic, phenotypic), which quantify the degree of biological aging relative to chronological age based on various DNA methylation patterns.[113] This study found that higher PBB levels were positively associated with age acceleration (intrinsic: $\beta=0.24$, 95% CI: 0.01, 0.46; extrinsic: $\beta=0.39$, 95% CI: 0.12, 0.65; phenotypic: $\beta=0.30$, 95% 95% CI: 0.05, 0.54 per natural log unit increase in PBB). Interaction with age at exposure was not detected; however, in stratified models, associations remained only for individuals exposed at ≤16 y of age, who may be more susceptible to endocrine disruption if exposed before or during puberty. Epigenetic age acceleration has been found in other research to be associated with EDC exposure[136] and several adverse health outcomes,[137] including breast cancer.[138]

Metabolomic differences. A cross-sectional analysis using serum samples collected from 2011–2014 examined metabolomic variations associated with PBB-153 in 156 participants in the Michigan PBB Registry (mean age: 39.7 y).[45] Biological functions associated with observed pathways were related to cellular respiration, essential fatty acids, and polyamine and catecholamine metabolism (pathways associated with neurodegenerative diseases, including Parkinson disease). Some differences were noted between generations. In the F0 generation, PBB-153 (a congener of PBB) levels were associated with pathways related to the microbiome, catabolism, and amino acid metabolism. In the F1 generation, PBB-153 levels were associated with pathways related to pro-inflammatory signaling lipids, fatty acid metabolism, nitrogen catabolism, and antioxidants.

A cross-sectional study[117] using serum samples collected from 2013 to 2014 of 498 individuals (mean age: 51.5 y) stratified by generation applied high-resolution metabolomics to identify biological responses to PBB exposure with a larger cohort and updated methodology from the previous metabolomics study.[45] Pathways associated with PBB levels in both generations were generally involved in energy metabolism, fatty acid metabolism, oxidative stress, and glycan metabolism. Some of these pathways are involved in neurodegenerative disease, adverse birth outcomes, and endocrine system function. Metabolic perturbations associated with PBB in the generation with direct dietary PBB exposure were related to oxidative stress (e.g., pentose phosphate and vitamin C metabolism), whereas perturbations in the generation exposed *in utero* and through breastfeeding were related to energy production (e.g., pyrimidine, amino sugars, and lysine metabolism).

Discussion

After the 1973–1977 PBB contamination of Michigan farms and food supply, the Michigan PBB Registry was assembled, has been maintained for 50 y, and includes multiple generations because of strong partnerships with the community. The Michigan PBB Registry has enabled researchers to explore the subacute, long-term, and multigenerational impacts of PBB exposure and to reevaluate findings with modern epidemiological methodology and a nuanced understanding of underlying biological mechanisms. Because the primary PBB exposure onset was relatively well-defined in 1973, studies have been able to explore specific sensitive periods of exposure during the life course to expand our understanding of the impacts of EDCs at different life stages. The large exposure contrasts within the cohort have also allowed for dose–response assessments that are seldom possible outside occupational settings. Strong community–academic partnerships have allowed this cohort to be followed across decades and multiple generations, allowing for investigation of chronic and transgenerational impacts from the perinatal period and across the life course. The PBB-affected community has helped guide recent studies to ensure that their continuing health concerns are included in the research.

Research on Acute and Subacute Effects in the F0 Generation

Early studies in the F0 generation were the first epidemiological and clinical investigations of the health effects of BFRs, a class of organohalogens now known to cause many adverse health effects.[139] Very little was known at the time of the possible health impacts of synthetic chemicals developed during the 20th century, and the concept of endocrine disruption from exposure to such chemicals had not yet emerged. Thus, investigators examined a wide variety of symptoms and conditions.

Several consistent methodological issues limited the interpretation of these early results. First, many chronic diseases have a long latency period, and some studies were limited by a shorter follow-up time than may have been required for certain conditions to

manifest, including reproductive outcomes (especially among individuals exposed as children), diabetes, cancer, and mortality. Next, many studies categorized exposure levels based on broadly defined groups with wide exposure ranges (e.g., by farm residence, farm product consumption, occupation, or geographic location) rather than by individual PBB measurements. Exposure to PBB was pervasive; therefore, within-group variability may have masked potential effects of PBB via exposure misclassification bias. Finally, the researchers mainly relied on univariate analyses, including *t*-tests and chi-square tests, and many did not report their statistical methodology, precluding a critical interpretation of their results. Most analyses in the early studies were unadjusted for covariates, likely introducing confounding bias.

Despite these limitations, several interesting findings inspired future investigation. Although dose–response relationships between PBB and symptoms were not established or not examined in many cases, several differences were noted between exposed Michigan residents and comparison groups, including elevated prevalence of abnormal liver function markers (SGPT, SGOT),[62] gastrointestinal tumor markers (CEA),[75] dermatological problems,[46,49,51,64] markers of altered immune response,[52,65,66] neurological symptoms,[46,49,68,71] and thyroid dysfunction.[46,74] Early studies on intergenerational PBB transfer[36,43,48] were foundational for future exposure modeling and assessment of perinatal impacts. Several early findings (e.g., thyroid dysfunction, digestive cancers, and immune impacts) were further explored in studies with longer follow-up periods, more sensitive exposure assessment, more sophisticated statistical methods, and guidance from a growing literature on EDCs, providing a fuller picture of both long-term and intergenerational health effects of PBBs, PCBs, and other EDCs, and POPs more broadly.

Research on Long-Term Effects in the F0 Generation

The examination of long-term health outcomes (1990–2020) among F0 individuals exposed via diet identified several outcomes of concern across biological systems, including altered thyroid hormone levels,[82,83] reduced liver function,[86] risk of breast and digestive cancers and lymphoma,[88,89] and altered menstrual cycle function and associated hormone levels.[93,94] Several studies of chronic outcomes among F0 cohort members were limited by relatively small sample sizes for specific outcomes, which could contribute to imprecision and risk of sparse data bias.[127] Future studies may be able to provide larger samples (e.g., higher case numbers for specific cancer types) in which to assess chronic health impacts of PBB exposure, thereby improving effect estimation.

Thyroid Function

Although studies among F0 participants have shown mixed results for the impact of PBB on thyroid function, more recent research highlights the importance of considering the timing of exposure relative to developmental windows. Yard et al. did not find higher odds of self-reported diagnosed thyroid disease with increasing PBB levels in an analysis of 3,333 registry members.[84] Conversely, Jacobsen, et al. found evidence supporting the association between PBB exposure with thyroid hormone levels and thyroid disease.[83] Curtis et al. extended this work and found that both PBBs and PCBs were associated with thyroid function, specifically in people exposed as children or prenatally.[84] These findings are also consistent with studies on PCBs[121,122] and PBDEs.[123–126]

Cancer

A study in 1976 of the cancer marker CEA found higher levels in workers with more than 5 y of employment at the plant that produced PBB and other chemicals in comparison with farmers.[75] Long-term studies among F0 cohort members found a suggestive, but not statistically significant, association between higher PBB levels and breast cancer.[89] The role of endogenous hormones and exogenous hormone replacement therapy in breast cancer is well-documented, making it biologically plausible that an EDC acting as a synthetic hormone could contribute to breast carcinogenesis.[140] More research is needed in the Michigan PBB Registry to determine whether cancer incidence rates were higher among chemical workers (who may have had high PBB exposures lasting several years), as well as among participants exposed to PBB *in utero*. There is substantial evidence that prenatal exposure to EDCs, including the estrogenic chemicals diethylstilbestrol (DES),[141,142] bisphenol A (BPA),[143,144] and DDT,[145–147] may predispose individuals to certain cancers later in life.[148] Recent EDC studies have suggested carcinogenic mechanisms through epigenetic changes,[144,149–151] immune dysregulation, chronic inflammation,[152–154] DNA damage,[155] oxidative stress,[23,156,157] disruption of sex hormones,[158–160] and disruption of thyroid hormones.[24,161] Studies of PCBs, the more widespread chlorinated analogs of PBBs, have found that different congeners act on endocrine-mediated processes through different mechanisms determined by their structure.[162] Some act as estrogen agonists, which appear to be most relevant for breast cancer and other reproductive effects. Other congeners are antiestrogenic, whereas some induce phenobarbital-type cytochrome P450 enzymes.[163] The mechanistic differences between PCB congeners and their impact on specific cancer types have limited the ability to make conclusions from epidemiological research lacking specific exposure or outcome data.[164] Different PBB congeners may also impact health through different mechanisms and with different potencies. Epidemiological[165,166] and toxicological[157,160] studies have found carcinogenic effects differentially associated with specific PBDE congeners, though evidence is not robust enough for a consensus on congener-specific effects for PBDEs.[167,168] The importance of different congeners to different health outcomes may need to be considered when comparing Michigan PBB Registry studies using enrollment PBB measurements, which measured total PBBs (comprising $\sim$60% PBB-153[118]) and more recent congener-specific measurements.[40]

Research on Effects in the F1/F2 Generations

As the years passed, researchers could examine PBB exposure's impact on subsequent generations from exposures via placenta and breastfeeding. Studies of the F1 generation benefited from the longitudinal nature of the Michigan PBB Registry, with clear temporality and exposure data for their F0 parents dating back to the years following the PBB contamination crisis. Higher maternal exposures were associated with an increased likelihood of male birth (similar to findings for some PCB congeners and the organochlorine pesticide metabolite DDE in two other cohorts[169,170]; a lower odds of male birth has also been found with some PCB congeners[170,171]), offspring with low Apgar scores (similar to some findings for DDT[172]), a more feminized 2D:4D digit ratio among female offspring (in contrast with null findings for the dioxin TCDD[173]), and male GU conditions. (Similar findings have been reported by some studies on dioxins, PBDEs, and organochlorine pesticides.[174]) Higher paternal exposures were associated with offspring with lower birth weight.[101] Relatively few studies have examined impacts of paternal chemical exposures on birth outcomes,[175] though toxicological research on paternal dioxin levels[176] and

epidemiological research on parabens[177] have reported higher risks of preterm birth; epidemiological research on paternal heavy metal exposures has also found adverse impacts on birth weight.[178] Within the Michigan PBB Registry, paternal PCB levels were found to have nonstatistically significant associations with preterm birth and lower birth weight.[101]

As adolescents, female F1 offspring with higher *in utero* and breastfeeding exposures had earlier age at menarche—a risk factor for breast,[179] ovarian,[180] and endometrial cancers[181]—as well as earlier pubic hair development.[105] There was a dose-dependent decrease in the heritability of both age at menarche and menstrual cycle length with increasing PBB levels.[133] Subsequent studies have found precocious female puberty after exposure to other potential endocrine disruptors, including phytoestrogens, PCBs, BPA, and some pesticides,[182,183] though some research has also found delayed breast and pubic hair development in girls with higher maternal POPs.[184] In contrast to precocious puberty among PBB-exposed female offspring, male offspring were more likely to report delayed puberty and growth. Delayed pubertal onset in boys was also subsequently reported with prepubertal exposures to coplanar dioxin-like PCBs and dioxin-like organochlorine pesticides in the Russian Children's Study.[185]

Menarche was earliest among girls who were breastfed by highly exposed mothers, which aligns with research showing that breast milk was an important source of early-life exposure to lipophilic POPs.[186] An early study in the Michigan PBB Registry found that PBB levels on a per-lipid basis were 100 times higher in women's breast milk than in serum.[48] Another study found that children of Registry-enrolled mothers who had detectable serum PBB and breastfed for $\geq$5.5 months were six times more likely to have detectable serum PBB in comparison with children who were not breastfed.[55] A study of menstrual cycle among F1 adults exposed to PBB *in utero* found higher levels of progesterone metabolites among women with higher estimated *in utero* PBB levels, though other menstrual cycle characteristics were not associated with PBB level.[110]

There has thus far been an insufficient sample size to study many pregnancy outcomes among F1 women; however, self-reported spontaneous abortions were higher with higher estimated *in utero* exposure levels.[100] PBB exposure at older ages did not appear to affect pregnancy loss; no difference was found in spontaneous abortion rates by PBB level in a larger group of women primarily exposed to PBB through contaminated food as adults, reinforcing the importance of the timing of exposures on health impacts.

Some analyses among F1/F2 cohort members may have been affected by imprecision and sparse data bias stemming from small numbers for specific outcomes. Selection bias may also be present, because F0 parents and F1 offspring with health concerns may have been more likely to participate in follow-up studies than original registry members without these concerns. Although studies from the early 2000s onward used improved laboratory methods with lower LODs, studies using enrollment PBB data have a LOD of 1.0 ppb. Given the evidence for nonmonotonic (e.g., U-shaped) dose–response relationships for some EDC–health associations, this higher LOD may have precluded detection of effects for lower exposure levels. The use of elimination models may have improved exposure assessment for perinatal health outcomes among F1 cohort members by accounting for different elimination rates by F0 maternal factors (e.g., smoking, BMI, breastfeeding, parity). As the cohort ages, future research should reexamine the incidence of specific cancers, examine effects among the F2 generation in relation to F0 and F1 PBB levels, and incorporate both health outcome and omics markers.

Epigenetic and Metabolomic Studies

Recent Michigan PBB Registry studies incorporating emerging omics approaches have highlighted potential biological pathways for health impacts observed in prior studies, particularly related to endocrine and immune function. These studies found higher PBB levels associated with accelerated biological aging among participants exposed at ages $\leq$16 y,[113] DNA methylation at CpG sites associated with estrogen and pathways related to immune function and endocrine-mediated autoimmune disease,[111] SEMs for pathways related to endocrine function and xenobiotic metabolism,[112] epigenetic alterations involved in sperm development,[116] and metabolomic variations.[45,117]

Exposures to persistent EDCs[187] beyond PBBs, including PCBs[188] and the organochlorine pesticide DDT,[189] were associated with altered gene expression in research outside the Michigan PBB Registry. These epigenetic changes have been proposed as a pathway to cancer.[144,150,151] EDC-related epigenetic changes have been linked to cancers of the breast,[190–192] prostate,[193–195] and thyroid,[196,197] among other adverse conditions. DNA-methylation–based metrics of biological aging, or "epigenetic clocks,"[198] are associated with a higher risk of chronic diseases, including cancers of the breast[199–201] and other sites.[138,200,201] Epigenetic alterations in target tissues are known to play a causal role in carcinogenesis, particularly for breast cancer.[202,203] PCBs, which are classified as carcinogens,[204] have been shown to be associated with DNA methylation in humans,[204–206] with evidence linking PCBs and carcinogenesis.[207] Within the Michigan PBB Registry, PCBs correlated with DNA methylation differences for DNA regions associated with immune function and xenobiotic metabolism.[208]

Although these novel methods have provided interesting insights into potential mechanisms, they are not without limitations. The cross-sectional nature of these studies (i.e., PBBs and mechanistic biomarkers were measured from the same blood sample), as well as the novelty and nonspecificity of the biomarkers examined, raises the possibility of reverse causality. It is possible that epigenetic or metabolomic changes are a consequence of PBB-associated health outcomes, rather than mediators along the path from PBB exposure to the development of health outcomes. The evolving nature of the field of omics research means that there is a lack of clear characterization for what many biomarkers represent. These studies were also limited to a specific subset of PBB registry participants who provided blood samples between 2003–2005, 2012–2015, or 2017–2020, and small samples may have limited analyses stratified by multiple factors such as generation, sex, and age at exposure. Newer laboratory methods also specifically measured PBB-153 and were generally unable to reliably measure other PBB congeners at lower concentrations. This is distinct from older studies that measured PBB mixtures, which were $\sim$60% PBB-153.

Relevance of Findings Beyond the Michigan PBB Registry

After nearly a century since their initial production, exposures to BFRs and POPs are widespread. Although PBB production stopped after the Michigan contamination event, PBB-153 was still detected in 77% of sampled Americans in the 2013–2014 NHANES.[39] Some BFRs, including most PBB and PBDE congeners, have long half-lives.[56,58] In a study conducted with members of the Michigan PBB Registry, levels were still significantly higher than the NHANES average; 60% of those tested had serum levels higher than the 95th percentile.[40] Among other BFRs, commercial PBDE mixtures PentaBDE and OctaBDE were withdrawn from the US market in 2004, and DecaBDE was phased out in 2013.[209] An analysis of NHANES data found only a slight

decline in Americans' total PBDE levels between surveys in 2005–2006 and 2013–2014 (between 10% and 20% for congeners PBDE-28, PBDE-47, PBDE-99, PBDE-100, and PBB-153), likely due to the use of old products containing PBDEs.[39] Due to similar chemical structures[26] and toxicological properties, PBBs can provide insight into the health impacts of newer chemicals, especially because the effects of replacements may not be known for decades.[210,211] In addition, leveraging the data from this unique multigenerational cohort can inform the broader evidence base for health impacts and biological mechanisms of other "legacy" POPs such as PCBs, dioxins, halogenated dibenzofurans, organochlorine pesticides, and some perfluoroalkyl substances (PFAS), which have contaminated water supplies and agriculture across the United States.[212]

Looking to the Future

The Michigan PBB Registry is a long-running multigenerational cohort that includes individuals with high exposures during different life stages, providing valuable information for the study of POPs and EDCs. Study of this unique cohort made possible the first observation of altered pubertal timing among males and females associated with *in utero* chemical exposure as well as the risk of subsequent pregnancy loss among females. Future research priorities should leverage this long follow-up to investigate chronic conditions with long induction periods, especially cancers, and other chronic conditions such as autoimmune, neurodegenerative, metabolic, and musculoskeletal conditions. Health impacts and trans-generational epigenetic inheritance in the F1/F2 generations are of particular interest, as well as metabolomic changes that may relate to disease risk.

The scientific contributions of the Michigan PBB cohort to environmental epidemiology and our understanding of EDCs and other environmental chemical exposures can guide future studies in formulating appropriate research questions grounded in mechanistic knowledge. The experience of this unique cohort adds to the growing evidence that the effects of EDCs—and environmental exposures generally—depend both on the dose and timing of exposure relative to developmental windows, with the most damaging effects resulting from exposures during fetal development and before puberty.[140] Fifty years after the tragedy of Michigan's PBB contamination, we have learned much about BFRs, POPs, and EDCs that can be applied to ongoing efforts to protect population health from harmful chemicals.

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Data are available on request through the Michigan PBB Registry at pbbregistry@emory.edu.

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