Annual Georgia Environmental Conference

Investigating the Potential Multi-generational Impact of Environmental Exposures on the Human Epigenome: Implications for the Southeast

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Abstract

Currently, the potential for environmental exposures to cause epigenetic changes in humans remains largely unexplored. Recent animal studies indicate that environmentally-induced epigenetic changes may be inherited by subsequent generations. If this holds true for humans, the public health implications are enormous.

This study, conducted by the Michigan PBB Registry at Emory University, investigates potential epigenetic changes within families affected by exposure to the persistent organic pollutant (POP) and endocrine disrupting chemical (EDC) polybrominated biphenyl (PBB). During the 1970s, an industrial accident exposed millions of Michigan residents to PBB, mostly through contaminated food.

This study explores whether epigenetic changes associated with PBB exposure are passed through paternal DNA of PBB-exposed men to their offspring. Eligible families (n=20) will include a grandfather who was highly exposed to PBBs, while neither his partner, child, child's partner, nor grandchild was directly exposed. Eligible families are identified through a review of PBB Registry records, community meetings, and phone interviews. Three generations from each family will provide blood samples to verify PBB exposure status and detect epigenetic marks. Participants' health conditions are recorded through a health questionnaire.

The results of this study will be significant to risk assessments for sites in the Southeast where POPs and EDCs are manufactured or present in environmental media. PBBs are toxicologically similar to other POPs and EDCs that are ubiquitous in the United States. Evidence of PBBs' epigenetic effects in humans may warrant further research into environmentally-induced epigenetic effects and the expansion of risk assessments to include multigenerational health effects.

Introduction

In the 1970s, the Michigan Chemical Company manufactured the persistent organic pollutant (POP) and endocrine-disrupting chemical (EDC) polybrominated biphenyl (PBB) at its plant in St. Louis, Michigan. In 1973, a PBB mixture was shipped from the plant in place of an animal feed supplement. PBBs were mixed into livestock feed, sent to farms throughout Michigan, and fed to livestock. Millions of Michigan residents consumed PBB-contaminated food until the oversight was identified a year later. The Michigan PBB Registry (the PBB Registry) was created to investigate the potential long-term health effects of this exposure.

FIGURE 1: Location of the former Michigan Chemical Company plant.

FIGURE 2: A stone marker at the former Michigan Chemical Company plant.

This research effort stems from concerns expressed by the PBB community regarding whether a man's exposure to PBB could affect the health of his children or grandchildren. This work is conducted in partnership with the PBB Citizen's Advisory Board, the Pine River Superfund Citizen Task Force, the Mid-Michigan District Health Department, and Alma College.

While PBBs are no longer produced in the U.S., POPs and EDCs that are toxicologically similar to PBBs are ubiquitous due to their many uses and persistence in the environment. Animal studies indicate that other EDCs cause changes in DNA expression that can be passed to offspring (epigenetic changes), but this has yet to be observed in humans. If PBBs are found to have a similar effect in humans, this could greatly affect how practitioners in the Southeast quantify health risks from POPs.

Methods

Objectives:

- **Measure DNA methylation as an indicator of epigenetic changes.**
- **Investigate any associations between DNA methylation patterns and individual PBB exposure among the Michigan PBB cohort.**

To determine if epigenetic marks caused by exposure to PBBs can be inherited in humans, this study includes descendants of PBB-exposed grandfathers rather than of PBB-exposed grandmothers. This ensures that any epigenetic changes seen in offspring are inherited, rather than a result of direct exposure in the womb or though ingestion of breast milk.

This study will compare the epigenetic patterns of 20 families in which only a grandfather was exposed to PBBs to 5 families in which no member has had significant PBB exposure. PBB exposure is defined as a serum PBB level above 0.19 parts per billion (ppb).

Epigenetic changes:
Changes in DNA expression that do not alter the DNA sequence itself. Epigenetic changes may be inherited by future generations.

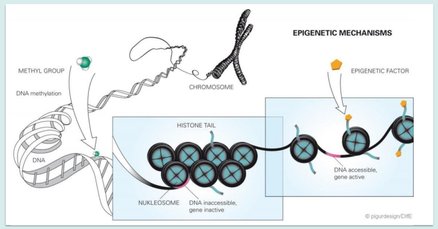

FIGURE 3: Epigenetic mechanisms.

Multiple sources are used to identify eligible PBB-exposed families:

- Families from the PBB Registry database are identified based on family members' previous PBB blood levels. Groups of particular interest include families of male former Michigan Chemical Company workers, males who lived on PBB-quarantined farms, and male Michigan residents who consumed PBB-contaminated food.
- Phone interviews are conducted by PBB Registry staff to determine family eligibility and to consent and enroll participants.
- Community meetings are held in Michigan 2 to 3 times per year to inform community members about opportunities to participate in this study. Interested community members are screened on-site for study eligibility. Trained phlebotomists collect blood samples from participants, and PBB Registry staff administer a health questionnaire to each adult participant.
- Information about each family, including family structure and individual PBB exposure history, is synthesized into family trees to maintain a comprehensive record of recruitment and to aid further recruitment of family members. Blood from each participant will be analyzed at Emory University for PBB exposure levels and epigenetic markers.

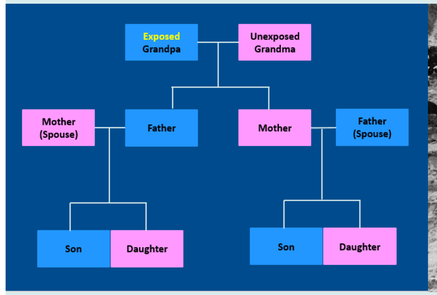

FIGURE 4: Family structure of "exposed" families in this study.

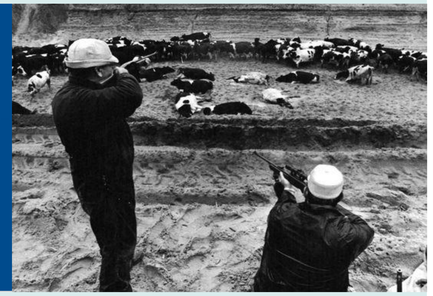

FIGURE 5: Cows sick from eating PBB are shot at a farm in Chase, Michigan.

Results

The PBB Registry's continued partnership with Michigan community members has yielded promising enrollment numbers thus far (Table 1). Recruitment for this study will continue during community meetings held in Michigan in September 2018.

TABLE 1: Cumulative Family Recruitment and Eligibility

Metric	Count[1]
Total number of families in which at least one person has participated[2]	19
All eligible families in which at least one person has participated	16
Eligible families with complete participation from all three generations	1
Goal for number of PBB-exposed families that have fully participated	20

Notes:
1. This table reflects families represented during the PBB Registry's December 2017 and April 2018 field events.
2. Participating families are counted here regardless of their eligibility for the study.

FIGURE 6: PBB research partners during a meeting in Michigan in April 2018.

Preliminary results include:

- Out of 20 PBB-exposed families required for this study, 1 family has completely participated.
- 15 additional eligible families have had at least one family member participate.
- The Michigan community continues to show extraordinary interest in this study. Community members regularly inquire about enrolling during community meetings, and via email and phone communications.

Conclusion

The Michigan PBB incident provides a rare opportunity to research the epigenetic effects of environmental PBB exposure in humans and offer valuable knowledge to the affected community. This research challenges the notion that *direct* exposure to environmental contaminants is necessary to modify health outcomes. If this study provides human evidence demonstrating that environmentally-induced epigenetic changes can be inherited by future generations, professionals working with sites in the Southeast where POPs are present should consider incorporating epigenetic, multigenerational effects into their risk assessments. As evidence mounts that environmental contaminants can alter the human epigenome, risk assessors, risk managers, and regulators in the Southeast will face the task of innovating new methods to accurately assess the resulting risks to human health.

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This research is funded by NIEHS Grant #R01 ES025775, Michele Marcus, P.I.
Additional funding for this presentation was provided by the Environmental Health Department at the Emory University Rollins School of Public Health.
Many thanks to the Michigan PBB Registry team for their support, and to the people of Michigan who inspire this work.

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