# Fetal Determinants of Adult Disease: Probabilistic Application of Genomic Tools for Pre- and Post-Remedial PDBE Exposures

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**Background**: Brominated fire retardants (BFR) are a diverse group of chemicals that include polybrominated biphenyls (PBBs), polybrominated dipenylethers (PBDEs), tetrabromobisphenol A (TBBPA), and hexabromocyclododecane (HBCD), and that have been attracting attention regarding environmental pollution and human exposure for the last two decades. Whereas the Michigan incident with PBBs has resulted in extensive toxicological and epidemiological studies, this issue was regionally confined. More recently, the environmental problems related to BFRs have become a matter of great urgency due to the marked increases of PDBE levels in human milk in Sweden, Japan and North America[1,2]. The levels in the latter are twice as high as those in the former. Moreover, the disclosure of toxicological data on BFR demonstrates that some BFR exhibit serious health effects, including thyroidogenic, neurological, estrogenic and dioxin-like activities. Based on sediment core trends and human tissue levels, the BFR trends (particularly PDBE) are not co-linear with those of PCBs and PCDD/F. This suggests that the subtle toxicological impacts of PDBE , PCB, and PCDD/F on ecological and human receptors may be temporally resolved using genomics tools[3].

**Rationale**: Substantial uncertainties in a number of important technical areas relevan to risk assessment and remediation of PBDE have been indicated[2,4,5]: (1) Environmental sources: Whereas the predominant BFRs used are octa-and deca-BDEs, the ambient environment contains elevated levels of the lesser brominated analogs, indicating the plausibility of a reductive debromination pathway. Evidence for this pathway is lacking. (2) Environmental fate: Even though concentrations in soil/water/air have become better characterized, there is limited information on the pathways of propagation of these concentrations from the sources to the various trophic levels and to human tissues or fluids. (3) Toxicological properties: Despite the plentiful toxicological data available, the development and interpretation of meaningful toxicological endpoints or biomarkers are lacking, particularly for non-cancer effects such as perturbation of cellular energy metabolism and altered gene expression due to subtle alterations in cellular redox potentials. (4) Human health risks: The analysis of direct or prenatal exposures to infants and young children requires further consideration, to develop toxicity benchmarks for potential adverse effects on development or the endocrine system.

**Hypotheses**: The governing hypothesis is that BFR impart trans-generational health effects in exposed populations that can be quantified in animal studies and validated in an exposed population using genomics tools targeting genes involved in energy metabolism and oxidative stress. Following probabilistic quantification of causal relationships, we further hypothesize that the predictive genomic biomarkers will allow for assessing the beneficial impact of engineered exposure mitigation measures.

**Vision:** The BFR Exposure Assessment Research (BEAR) Program aims to develop predictive biomarkers, bioavailability indicators, and multi-media geographical exposure indices, relevant to trans-generational health effects from PBDE, as an exemplar group of compounds for a broader class of BFR with similar physical-chemical properties.

**Methodological Integration of the BFR Exposure Assessment Program**:
The Program capitalizes on expertise in environmental epidemiology, environmental toxicology, and environmental engineering, which is integrated in a data-stream-oriented research structure. The research tasks are organized such that the datasets generated from the various programmatic projects can be mined using bioinformatics tools and interpreted using multimedia environmental modeling, pharmacokinetic analysis and spatio-temporal statistical modeling techniques.

Data transfer between cores will take place in a stochastic framework, allowing for the uncertainties associated with one analysis to be incorporated into subsequent work. Such an approach will yield an objective representation of the overall uncertainties inherent in the problem, allowing for best estimates as well as meaningful confidence intervals to be identified at each stage of the project.

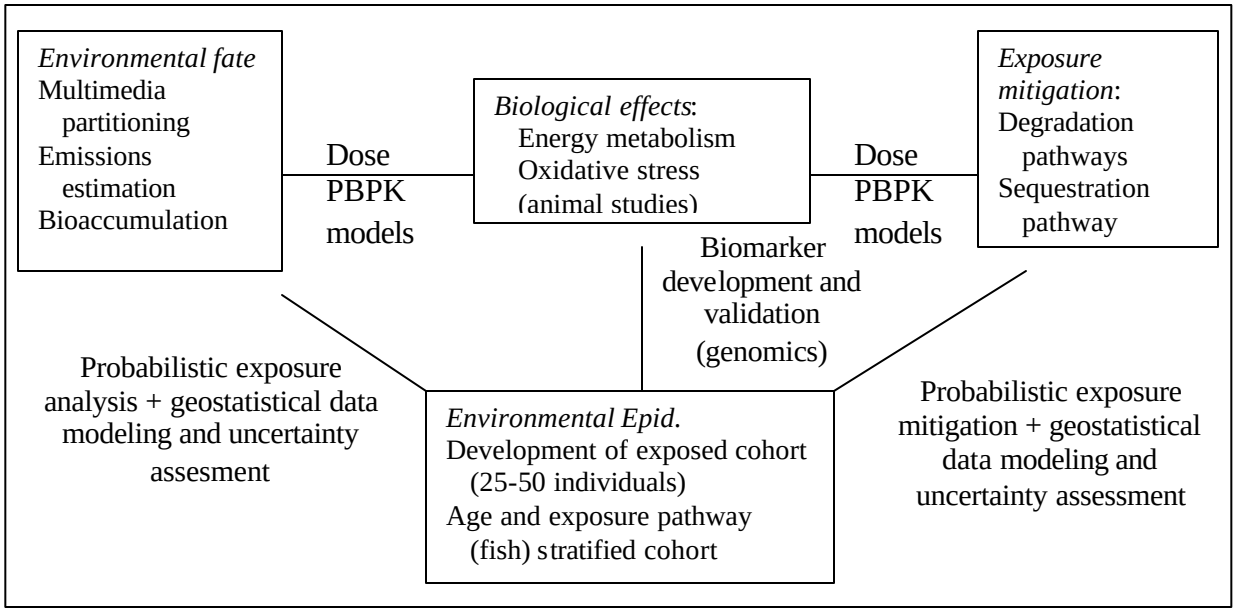


*Figure 1. Data flow model for BEAR Program*

The (i) source and ambient concentrations, (ii) bioavailable concentrations, (iii) acute toxicity reference values, and (iv) theoretical lifetime chronic intakes will be used to derive the toxicological effects from exposure doses. The BEAR Program will focus around a dose-effect paradigm that will allow for observation of short-term (hr-d) acute effects, and long term (mo.) chronic effects (Figure 2).

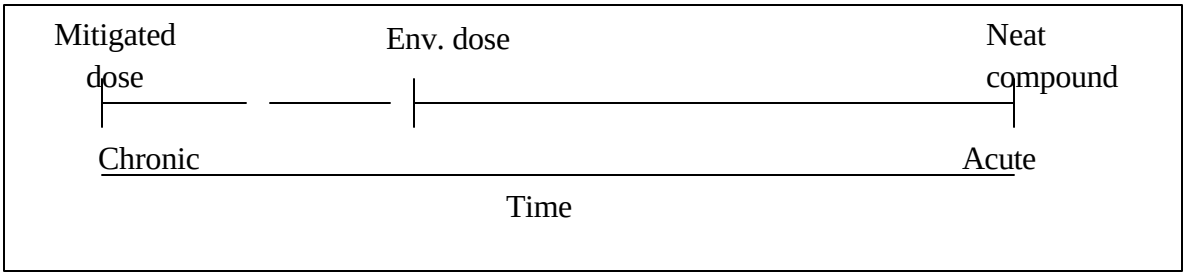


*Figure 2. Dose-effect paradigm for the BEAR Program*

**BEAR Program Structure:**

The focus of the PBDE exposure and health assessment will initially be on BDE 47 (2,2',4,4'-tetrabromodiphenyl ether), either as a single congener or as an intermediate product formed during reductive debromination of BDE 99 (2,2',4,4',5-pentabromodiphenyl ether), BDE 100 (2,2',4,4',6-pentabromodiphenylether), or BDE 209 (decabromodiphenylether). Later, both organic (e.g. PCB, PCDD/F) and inorganic (e.g. Hg) co-contaminants will be added to evaluate additive or synergistic effects.

***1. Environmental Exposure and Mitigation***

Objective: Quantification of environmental reactivity, environmental bioavailability, and trophic chain transfer of individual PDBE congeners with emphasis on lesser brominated congeners, resulting from abiotic/biotic debromination of BDE-47.

Approach: The reactivity of relevant environmental concentrations of BDE 47, BDE 99, BDE 100, and BDE 209 will be subjected to biotic (sediment microbial elutions; intact sediments) and abiotic (zerovalent metals, metal sulfides) catalytic activity under reducing conditions representative of freshwater, estuarine and marine environments to develop prevailing debromination pathways and their associated kinetics. Emphasis will be placed on pathways producing BDE 47 from higher brominated congeners, and on the production of mono- to triBDEs. The impact of debromination on bioavailability and toxicity is asessed using the Ah-receptor response assay. Fugacity-based models are used to describe and predict the phase transfer and trophic fate transfer of the parent compounds and debrominated intermediates to develop environmental bioavailability endpoints for relevant exposure pathways (biota, water, air) considered in the risk quantification and exposure assessment projects.

Deliverables: Bioavailability endpoints; Reactivity/fate endpoints

***2. Risk Quantification and Exposure Assessment***

Objective: This core will quantify exposure risks and their associated uncertainties in the presence and absence of mitigation measures.

Approach: The analysis is conducted in a probabilistic and geostatistical framework, incorporating uncertainties in relevant environmental parameters and their spatial and temporal distributions. A geostatistical framework will allow for the joint distribution of a variety of parameters to be analyzed by taking into account their individual spatial and temporal correlation structures as well as correlations among parameters and dependence on auxiliary variables. Geostatistical methods are then used for estimating contaminant exposure risk distributions, for estimating dose response functions using epidemiological data, and for exposure assessments to be used by the epidemiological project. Physiologically based pharmacokinetic modeling will be applied to evaluate PBDE bioaccumulation in human tissues and organs resulting from environmental exposure; these model results will be used in combination with the biological effects studies to predict the human health impact of PBDE exposure at environmentally relevant concentrations. Finally, geostatistical methods will be applied to define spatial disease risk distributions and estimate cumulative environmental contaminant loads.[6]

Deliverables: Pharmacokinetics /Exposure kinetics; Probabilistic exposure metrics

***3. Biological Effects***

Objective: Assessment of genes regulated by redox-sensitive transcription factors such as SP1, AP1 and NRF-2 and examination of the functional consequences of expression of novel genes in response to challenge by PBDEs. Additional analysis of direct pathophysiological consequences of cellular oxidative stress and altered energy metabolism following prolonged oral administration at critical windows of development *in utero* and in cross-fostered naïve offspring nursed by exposed and unexposed dames.

Deliverables: Development of predictive biomarkers

***4. Environmental Epidemiology***

Objective: 1) to characterize the distribution of PBDEs (and other environmental toxins such as dioxins, PCBs, and mercury) in blood in a defined exposed population; 2) to explain sources of variation of these chemicals in blood, such as age, gender, body mass index, diet, occupation, and residential history; 3) to assess possible clinical effects on endocrine function, such as indices of thyroid function and sex hormone function; and 4) to test and validate genomic markers identified in animal studies.

Deliverables: Validation of genomic biomarkers

**References**

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