How Does ORD Research on MOA Contribute to the Human Health Risk Assessment for PBDE Mixtures?

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LTG 1 Poster 06

Science Questions

- **Can the mode of action for PBDEs and other structurally related persistent chemicals be identified for the nervous system, reproductive system, and for endocrine effects?**
- **Does the route/pathway of exposure impact the toxicity of PBDE mixtures, and if so, what is the main exposure route?**
- **Do strain/species/gender differences in the toxicokinetics of PBDEs correlate with adverse health effects?**

Research Goals

Research conducted in ORD, other federal agencies, and academic institutions has shown that persistent organic pollutants (POPs) are a human health concern. For the last several years, ORD research has shown that polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs), dibenzo-furans (PCDFs), and perfluorinated chemicals (PFCs) produce a multitude of health effects on the nervous, immune, reproductive, and endocrine systems. While PCBs have been shown to cause adverse health effects in humans and rodents, few such evaluations have been conducted with polybrominated diphenyl ethers (PBDEs). PBDEs belong to the same class of POPs as PCBs and are widely used as flame retardants. As with PCBs, PBDEs are accumulating in the environment, and in humans. They have shown an exponential increase over the past few decades. The persistence and bioaccumulative characteristics of PBDEs, as well as their similarities to known toxic PCBs, raises concern over potential human health effects, especially in the developing organism. Understanding the mode of action (MOA) and toxicokinetics of PBDEs will not only inform their risk assessment, but also support risk assessment of POPs in general.

Findings and Conclusions

The MOA of PBDEs may be similar to non-coplanar PCBs for several neurotoxicity endpoints at equimolar concentrations.

PBDEs can activate genes within the CAR/PXR pathway, thus altering enzymes involved in thyroid hormone homeostasis.

House dust appears to be the major route of exposure for Americans.

Young mice and rats, who appear to be at the most susceptible stage for reproductive and neurotoxicity, appear to handle PBDEs similarly.

Toxicokinetic studies demonstrated that patterns of bromine substitution play a major role in the absorption, distribution, metabolism, and excretion of PBDEs in mice.

The observed effects on pubertal development are due to the ability of some of the congeners to act as competitive antagonists of the androgen receptor (AR).

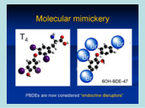
Methods/Approach

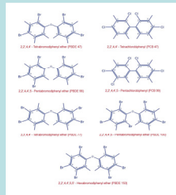
Mode(s) of Action

Structural similarities between PBDEs and PCBs:

PBDEs exist as 209 possible congeners based on number and position of halogens like PCBs. Unlike some PCBs that are coplanar, all PBDE congeners are non-coplanar in nature.

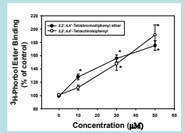
PBDEs also have structural similarities with T4.

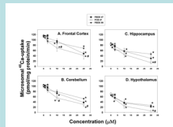




Calcium signaling:

PBDEs (mixtures as well as congeners) alter several neurochemical end points at concentrations similar to PCBs.

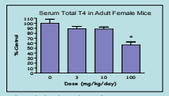




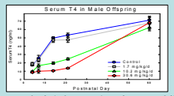
Thyroid Hormone Dysruption:

- Thyroid hormones are essential for proper metabolism, neurodevelopment, and differentiation of all cells of the human body.
- Adult mice exposed acutely to BDE 47 and rats exposed perinatally to DE-71 have decreases in serum thyroxine (T4).

BDE-47



DE-71



- TH perturbations in adults by chronic exposure may lead to thyroid hyperplasia/adenoma/carcinoma while developmental TH perturbations may cause neurological and reproductive effects..

Neurotransmitters:

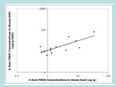
Preliminary data show increases in cortical dopamine levels in the same mice where developmental neurobehavioral effects were observed.

Exposure

Early life:

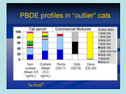
Transplacental
Breast milk
Indoor environment including house dust

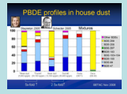
Breast Milk vs. Dust (ug PBDE/g dust; Penta-like congeners only; Wu et al., 2007)



Later life:

Combined exposure to the indoor environment and household dust





PBDEs in U.S. Household Dust resembles those in cats

Concurrent oral exposure to PBDE-contaminated food sources:

Market Basket Survey of U.S. Food
Schecter et al., Environ Hlth Persp 114: 1515-20(2006).

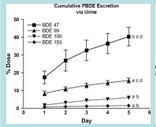
- Measured 13 individual PBDE congeners.
- 62 food samples purchased from three Dallas, Texas supermarket chains in 2003.

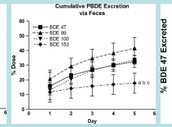
	Sum PBDEs Median (ppt, ww)
Fish N=24	616
Meat N=18	190
Dairy N=15	32.2
Miscellaneous N=5	84-2835

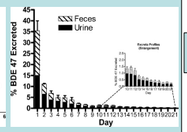
Toxicokinetics

BDE 47, 99, 100, and 153 in adult mice:

- All BDE congeners distribute with similar patterns into lipophilic tissues. Disposition is dictated by lipophilicity as adipose and skin were major depot tissues.
- Tissue conc. were higher for BDE-153 than for 100, 99, and 47, respectively.
- Excretion rates were inversely related to tissue conc. BDE-47 was the most rapidly excreted congener in urine and feces, largely as parent.
- Elimination is biphasic with initial half-lives of 1-3 days, but terminal half-lives were longer, suggesting potential bioaccumulation.







BDE 47 in Developing mice:

- Toxicokinetics of BDE 47 are different in infantile than in adult mice due to lack of a major urinary protein prior to puberty.
- Tissue concentrations of BDE 47 are higher in pups as compared to adults because of reduced capacity to excrete BDE 47 in urine.
- These differences lead to higher concentrations of BDE 47 at target tissues (e.g., brain) during critical windows of development.

Species Difference: Rats vs Mice:

- BDE 47 is slowly eliminated in rats whereas adult mice undergo a much more rapid initial excretion of this congener suggesting active urinary elimination.
- However, young mice and rats, who appear to be at the most susceptible stage for reproductive and neurotoxicity, appear to handle the chemical similarly.
- Raises the question of which species/life stage is a better model for human risk assessment. There is no evidence of parent PBDEs in human urine.

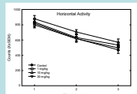
Effects

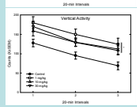
Neurotoxicity: An acute exposure in infantile mice to BDE47, during a period of rapid brain development, produced behavioral alterations that were observed as long as 4 months later.

Changes in neurotransmitter systems may explain these effects. Preliminary data showed increases in cortical dopamine levels in these same mice.

Serum thyroid hormone levels (T3 and T4) were shown to be unaltered with this dosing paradigm, suggesting these findings are not secondary to thyroid disruption.

These findings enabled IRIS to consider these effects as critical in the risk assessments.

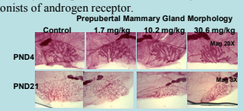




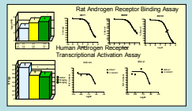
Reproductive effects: DE-71 delayed the age of onset of preputial separation (PPS) and suppressed the growth of androgen-dependent tissues in the Wistar rat following peri-pubertal exposure. We also observed a delay of PPS following developmental exposure to DE-71.

These effects were mediated via the androgen receptor, as some PBDE congeners in DE-71 (PBDEs 47 and 100) were competitive antagonists of androgen receptor.

PBDEs altered mammary gland development



Male Reproductive Effects



Hepatic effects: BDE 47 and the commercial penta mixture DE-71 are agonists for the nuclear receptors CAR and PXR which regulate genes involved in the hepatic metabolism of xenobiotics

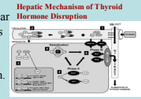
Genes involved include Cytochrome P450s, UDPGTs, Sulfurtransferases, and transporters. The resulting enzymes can conjugate and transport thyroid hormones, potentially altering elimination.

Possible mechanisms of thyroid hormone disruption include:

A. PBDEs displaces thyroid hormones from transthyretin, a serum binding protein;
B. PBDEs induces Phase II enzymes, Phase III transporters, and decrease deiodinase 1 ;
C. Overall effects result in an increase in thyroid hormone elimination

PBDEs found in household dust were **equally** or more **bioavailable** than PBDEs dissolved in oil when fed to rats as part of the diet.

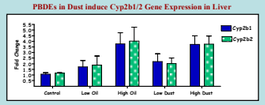
Hepatic Mechanism of Thyroid Hormone Disruption



Correlations Between Hepatic P450 Gene Expression and Concentration of PBDE Homolog Groups

Cyp2b1	Tetra-Hexa	Sig. $R^2=0.27$
Cyp2b1	Hepta-Deca	Sig. $R^2=0.61$
Cyp2b2	Tetra-Hexa	Sig. $R^2=0.33$
Cyp2b2	Hepta-Deca	Sig. $R^2=0.17$

PBDEs in Dust induce Cyp2b1/2 Gene Expression in Liver



Impact and Outcomes

This research will help address uncertainty in risk assessment/management for PBDEs. The results have indicated that the PBDEs are more toxic than previously thought, with the greatest concern being for the developing organism. The increased understanding that dust is a major exposure route has raised concern about exposure of children to these compounds.

- Provided NCEA with data demonstrating long-lasting neurobehaviorial effects from a single exposure during development that was used in one or more IRIS assessments (BDE47 – CASRN-5436-43-1; BDE99 – CASRN-60348-60-9; BDE153 – CASRN-68631-49-2)
- Provided Agency with exposure and effects research for enhanced sources, exposures, toxicokinetics, and effects of PBDEs that will be used for designing and implementing future research.

Future Directions

There is a need for risk assessment purposes to assess pharmacokinetic and effects research for Hexabromocyclododecane (HBCD), another major BFR of concern to IRIS whose use has been increasing with the phase-out of the PBDEs. Studies on the pharmacokinetic behavior of HBCD in mice are in progress, as are its effects on thyroid hormone disruption.

There is a need to determine if there is any linkage between PBDE exposure and thyroid disease in adults.

Researchers Involved

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Use of Mechanistic Data in Risk Assessment

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