Research Brief 175: Do Mirror Differences Among Non-coplanar PCBs Influence Their Developmental Neurotoxicity?

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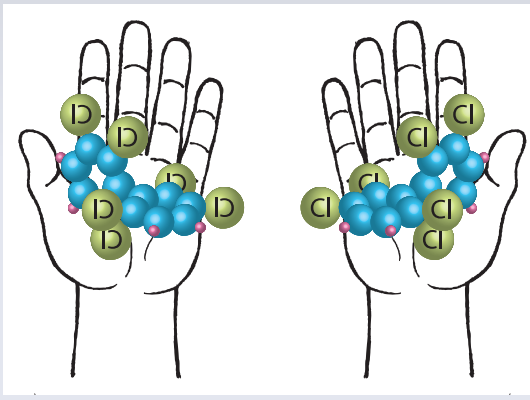
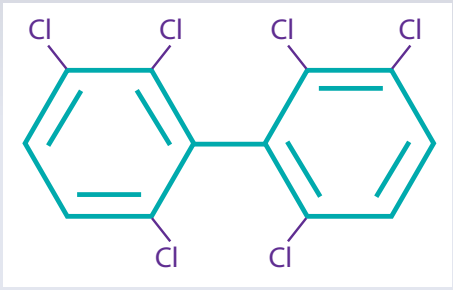
Background

Human epidemiological data suggest a positive association between developmental exposure to polychlorinated biphenyls (PCBs) and behavioral/cognitive deficits in infancy or childhood. Specifically, *in utero* and lactational PCB exposures correlate with decreased IQ, impaired learning and memory, attentional deficits, and lowered reading comprehension. Comparable behavioral deficits are observed in primate and rodent models following developmental PCB exposures. Experimental data indicate that this developmental neurotoxicity is related to the number and location of chlorine substituents of the PCB congener. Data also suggest that intracellular calcium (Ca^{2+}) channels may be the most sensitive target of toxicity.



PCB 136 Enantiomers

Of the 209 PCB congeners, 19 exist as pairs of enantiomers – structures that, like the right and left hand, are complete mirror images but cannot be superimposed over one another. The mirror images are chemically identical, but the chlorines differ in their orientation in space. Enantiomers differ from each other and from the racemic mixture (a mixture with a 1:1 ratio of both enantiomers) in their interactions with biological targets. As seen below, PCB 136 (2,2',3,3',6,6'-hexachlorobiphenyl) is one of these congeners. This environmentally relevant, neurotoxic compound exists as two mirror images, but one preferentially undergoes enrichment in the environment which results in a shift from a racemic mixture to mixtures predominated by one of the enantiomers.



PCB 136 Molecular Structure

Emerging human biomonitoring data suggest significant variability in the enantiomeric enrichment of PCBs in the human population. This raises the question of whether enantiomeric enrichment influences the risk for adverse neurodevelopmental outcomes following PCB exposure. An ongoing collaboration between the Superfund Research Programs (SRP) at The University of Iowa and the University of California, Davis, investigates this important question.

Advances

Dr. Lehmler's laboratory at the University of Iowa has tested this hypothesis by examining the enantioselective binding of PCB 136 atropisomers (designated (+)-PCB 136 and (-)-PCB 136) to cytochrome P450 enzymes. The family of cytochrome P450 enzymes (CYP P450) is responsible for the biotransformation of many toxic substances. Using microsomal preparations containing three CYP P450 isoforms (CYP1A1, CYP2B, and CYP3A), the investigators showed maximal binding of both PCB 136 atropisomers in microsomal preparations containing high levels of cytochrome P450 2B. Most importantly, (+)-PCB 136 binding was greater than that of (-)-PCB 136 in all microsomal preparations investigated. These selective interactions of PCB 136 atropisomers are thought to result in the accumulation of (+)-PCB 136 in the liver and brain of mice.

In parallel, Dr. Pessah's laboratory at the UC Davis SRP demonstrated that (-)- and (+)-PCB 136 have differential effects on the ryanodine receptors (RyR1 and RyR2), which mediate the intracellular release of Ca^{2+}. This provides evidence of vastly different biologically activity for two PCB structures that differ only in how their chlorines orient in space. Using preparations of RyR1, they showed that (-)-PCB 136 could trigger Ca^{2+} efflux, whereas (+)-PCB

136 had no effect. (+)-PCB 136 also could not block the activity of (-)-PCB 136. The effect of (-)-PCB 136 was inhibited by an RyR antagonist, which confirmed that the Ca^{2+} efflux effect was due to (-)-PCB 136's action at the RyR.

Finally, to verify that (-)-PCB 136 could act at the RyR in intact cells, they showed that the (-)-, but not the (+)-PCB 136 enantiomer could enhance caffeine-induced intracellular Ca^{2+} transients in human embryonic kidney (HEK 293) cells.

Significance:

Together the data demonstrate enantiomer-selective interactions of an environmentally relevant PCB congener with cellular components, suggesting that the coincidence of preferential accumulation and differential activity of PCB atropisomers must be taken into account in evaluating their toxic potential.

For More Information, Contact:

Hans-Joachim Lehmler, Ph.D.
The University of Iowa
Department of Occupational and Environmental Health
100 Oakdale Campus, #221 IREH
Iowa City, IA 52242-5000
Telephone: 319-335-4211
Email: hans-joachim-lehmler@uiowa.edu

Isaac Pessah, Ph.D.
Molecular Biosciences
Univeristy of California, Davis
One Shields Avenue
Davis, CA 95616
Telephone: 530-752-6696
Email: inpessah@ucdavis.edu

To learn more about this research, please refer to the following sources:

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