IS THERE A MECHANISTIC BASIS TO COMBINE NON DIOXIN-LIKE PCBs AND PBDEs FOR HUMAN RISK ASSESSMENT?

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Introduction

Many food items, including human milk, contain PCBs as well as PBDEs at levels that have been reasons for concern from a risk assessment point of view. Based on the mechanisms of action within the group of PCBs a separation has been made for those congeners that activate the AhR-receptor, causing dioxin-like effects, and those causing effects via other biochemical or molecular mechanisms. This differentiation is primarily based on the possibility of a planar conformation of the biphenyl molecule in which chlorine substitution on the *ortho* positions is of crucial importance. PCBs containing none or only one chlorine atom on these *ortho* positions may exhibit dioxin-like effects. However, PCBs with one or more *ortho* chlorine substitutions cause very different effects, e.g. in the liver or the brain.

The dioxin-like (DL) PCBs are already included in the TEF concept in which additivity with PCDDs and PCDFs is generally accepted and used as a default approach for risk assessment. In this system each dioxin-like compound is assigned a TEF value that is multiplied with its actual concentration in the food item, which results in a specific amount of toxic equivalents (TEQs). For the non dioxin-like (NDL) PCBs with their *ortho* chlorine substitution patterns such a TEF system is not available. Threshold values for risk assessment have been derived using the total sum of PCBs.

PBDEs are also commonly occurring in the human food chain and most if not all the congeners present also have an *ortho* bromine substitution pattern, thereby resembling NDL-PCBs. In this presentation a critical review is given with respect to similarities or dissimilarities in the mechanism of action of non NDL-PCBs and environmentally common PBDEs. The major focus of this systematic review on mechanisms of action is on the PXR/CAR interaction in e.g. liver cells, modulations of functions of neuronal cells and interactions on the level of thyroid hormones and steroidogenesis. Effects on these endpoints will be discussed for the parent compounds, as well as for a limited number of human relevant hydroxylated metabolites of PCBs and PBDEs.

Methods

A literature search was performed for peer-reviewed articles in the scientific literature that address toxicity and biological effects of NDL-PCBs and/or PBDEs using the PubMed database of the US National Library of Medicine. The selection of NDL-PCBs and PBDE congeners included in this review are those that have been detected in human milk in global surveys from the World Health Organization (WHO), including 52 countries, between 2000 and 2010.

In addition, a number of key studies describing exposure to NDL-PCBs and PBDE congeners were also used. Based on this quantitatively most important NDL-PCBs were: PCB-28, PCB-52, PCB-101,PCB-138, PCB-153 and PCB-180[1,2] (El Majidi, Bouchard et al. 2014, Lee, Kim et al. 2013). For the PBDEs these were: BDE-28, BDE-47,BDE-99,BDE-100, BDE-153, BDE-154, BDE-183 and BDE-209[3-5]

Studies in which PCB or PBDE congeners induced CYP1A1 activity were excluded from this review, as this indicates the presence of a dioxin-like congeners[6]. Table 1 shows search terms that were used for this review, including the number of hits found in February 2014.

Table 1. Search terms used in Pubmed and associated number of hits for NDL-PCBs and PBDEs.

Key words used in Pubmed	Number of hits	Date
((polychlor* OR PCB OR NDL-PCB) OR (polybrom* OR PBDE)) AND (neurodev* OR neurotox*)	687	10/02/2014
((polychlor* OR PCB OR NDL-PCB) OR (polybrom* OR PBDE)) AND (nervous system)	813	10/02/2014
((polychlor* OR PCB OR NDL-PCB) OR (polybrom* OR PBDE)) AND (Ca2+ OR Calcium OR Ca OR calcium homeostasis) NOT fish	1130	10/02/2014
((polychlor* OR PCB OR NDL-PCB) OR (polybrom* OR PBDE)) AND (RyR OR ryanodine)	39	10/02/2014
((polychlor* OR PCB OR NDL-PCB) OR (polybrom* OR PBDE)) AND (neurite outgrowth)	6	10/02/2014
((polychlor* OR PCB OR NDL-PCB) OR (polybrom* OR PBDE)) AND (neurobehav*)	156	10/02/2014
((polychlor* OR PCB OR NDL-PCB) OR (polybrom* OR PBDE)) AND (thyroi* OR thyrox*)	806	10/02/2014
((polychlor* OR PCB OR NDL-PCB) OR (polybrom* OR PBDE)) AND (PXR OR pregnane OR nuclear receptor)	826	10/02/2014
((polychlor* OR PCB OR NDL-PCB) OR (polybrom* OR PBDE)) AND (CAR OR CYP OR P450)	666	10/02/2014
((polychlor* OR PCB OR NDL-PCB) AND (polybrom* OR PBDE)) AND (neurodev* OR neurotox*)	52	10/02/2014
((polychlor* OR PCB OR NDL-PCB) AND (polybrom* OR PBDE)) AND (nervous system)	43	10/02/2014
((polychlor* OR PCB OR NDL-PCB) AND (polybrom* OR PBDE)) AND (Ca2+ OR Calcium OR Ca OR calcium homeostasis) NOT fish	82	10/02/2014
((polychlor* OR PCB OR NDL-PCB) AND (polybrom* OR PBDE)) AND (RyR OR ryanodine)	2	10/02/2014
((polychlor* OR PCB OR NDL-PCB) AND (polybrom* OR PBDE)) AND (neurobehav*)	15	10/02/2014
((polychlor* OR PCB OR NDL-PCB) AND (polybrom* OR PBDE)) AND (thyroi* OR thyrox*)	86	10/02/2014
((polychlor* OR PCB OR NDL-PCB) AND (polybrom* OR PBDE)) AND (PXR OR pregnane OR nuclear receptor)	38	10/02/2014
((polychlor* OR PCB OR NDL-PCB) AND (polybrom* OR PBDE)) AND (CAR OR CYP OR P450)	26	10/02/2014
((polybrom* OR PBDE OR BDE) OR (polychlor* OR PCB OR NDL-PCB)) AND (hydroxylated OR OH) AND (neurotox* OR neurodev* OR neurobehav* OR thyroi* OR thyrox* OR CAR OR PXR OR nuclear receptor OR calcium OR ca OR CYP OR ryanodine)	283	19/05/2014

Results and discussion

A number of common endpoints were identified for NDL-PCBs and PBDEs. These included effects like disturbance of intracellular calcium homeostasis, neurobehavioral endpoints (e.g. spontaneous activity and learning ability), thyroid hormone related endpoints (T3, T4 and TS), and effects on the CAR/PXR receptors.

Calcium (Ca^{2+}) is an important agent in signal transduction in neuronal cells and has been shown to be involved in different cellular and subcellular processes such as, transmission of an action potential, exocytosis, cell death and mitochondrial function. Several studies showed effects of PCBs and PBDEs after pre- or postnatal exposure on neurobehavioral endpoints, like spontaneous activity, in rodents. Additionally, exposure to PCBs and PBDEs caused impaired spatial learning and memory abilities in both rats and mice. Multiple studies have also shown effects of both NDL-PCBs and PBDEs on the thyroid hormone homeostasis. In this respect, it is interesting to note that hydroxylated metabolites of both groups of compounds can also inhibit the binding of the thyroid hormone to its transport protein TTR. The constitutive androstane receptor (CAR) and pregnane X receptor (PXR) both have a function in metabolism of xenobiotics and can be activated by e.g. pharmaceutical, steroids and environmental chemicals. Chronic activation of CAR or PXR has been linked to adverse health effects. Experimental studies have shown that both NDL-PCBs and PBDEs are able to directly activate PXR and CAR and transcription of target genes.

It should be noted that many of the above endpoints are involved in mammalian developmental processes. In table 2 an overview is presented of the number of studies, categorized by endpoint and congener. Furthermore the qualitative type of effect - an increase, decrease or no effect - are presented in different colors. Overall, comparable effects were found on most endpoints that were studied. However for a particular effect lowest effect concentrations for these NDL-PCBs and PBDEs may differ up to one order of magnitude between different studies.

Based on this review of available scientific information it is concluded that human risk assessment may benefit from a combined approach for non dioxin-like PCBs and PBDEs for human risk assessment. However, the question is if the (human) risk assessment of both groups of compounds should actually be done using only the congener-specific concentrations only, or that the development of a separate toxic equivalency system is warranted.

Table 2: Overview of effects on endpoints of NDL-PCBs and PBDEs and some selected hydroxylated congeners. Red indicates an increase, blue a decrease and purple a lack of effect. The numbers indicate the number of articles that showed the same effect by a specific congener on t particular endpoint.

Endpoints	BDE 47	BDE 99	BDE 100	BDE 153	BDE 154	BDE 183	BDE 209	Ortho -OH	Para -OH	Meta -OH	PCB 28	PCB 52	PCB 101	PCB 138	PCB 153	PCB - 180	Ortho -OH	Para -OH	Meta -OH
Basal calcium	2 1	1	1					2	1	2		2 1		2	1	1			1
Spontaneous behavioral activity	3 1	4 1 1		1 1		1	2					1 1		1	2	1 1		1	
Learning ability	1											1		1	1	1			
[T_4] total	2 1	2 2					2 2			1	1		3		1 7 1			3	
[T_4] free		2 1											1		2			2	
[T_3]	3	2					2				1		3		2 3			1	
[TSH]	1						2						3		4			1 1	
CAR/PXR activation															1				

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References

1. El Majidi, N., Bouchard, M. and Carrier, G. (2014); *Chemosphere* 98: 1-17.
2. Lee, S., Kim, S., Lee, H.K., Lee, I.S., Park, J., Kim, H.J., Lee, J.J., Choi, G., Choi, S., Kim, S., Kim, S.Y., Choi, K., Kim, S. and Moon, H.B. (2013); *Chemosphere* 93: 1578-1585.
3. Frederiksen, M., Vorkamp, K., Thomsen, M. and Knudsen, L.E. (2009); *Int. J Hyg Envir Health* 212:109-134.
4. Ni, K., Lu, Y., Wang, T., Kannan, K., Gosens, J., Xu, L., Li, Q., Wang, L. and Liu, S. (2013); *Int. J Hyg Envir Health* 216: 607-623.
5. Gascon, M., Fort, M., Martinez, D., Carsin, A.E., Forns, J., Grimalt, J.O., Santa Marina, L., Lertxundi, N., Sunyer, J. and Vrijheid, M. (2012); *Environ Health Persp.* 120: 1760-1765.
6. Peters, A.K., Van Londen, K., Bergman, A., Bohonowych, J., Denison, M.S., Van Den Berg, M. and Sanderson, J.T.(2004); *Toxicol. Sci.* **82**: 488-496.