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Persistent Toxic Burdens of Halogenated Phenolic Compounds in Humans and Wildlife

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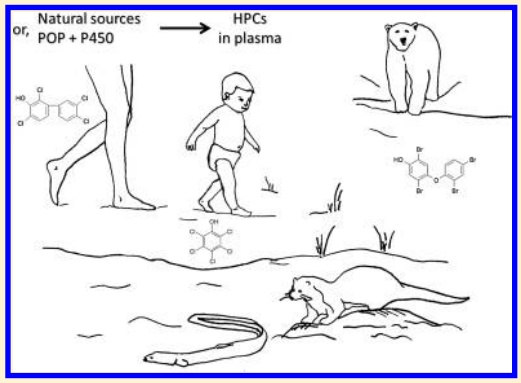
Supporting Information

ABSTRACT: Halogenated phenolic compounds (HPCs) including hydroxylated polychlorobiphenyls (OH-PCBs) and hydroxylated polybromodiphenyl-ethers (OH-PBDEs) can be persistent organic pollutant (POP) metabolites or natural marine compounds. Structurally similar to thyroid hormones (THs), they are retained in blood, transported through selective barriers, and the cause of endocrine and neuronal POP effects. This study presents a meta-analysis of HPC burdens in human and wildlife tissues, including OH-PCBs, OH-PBDEs, Pentachlorophenol, and polybromophenols. HPC blood plasma levels were also compared to known *in vitro* and *in vivo* toxicological effect concentrations. Blood, highly perfused, and fetal tissues contained the highest levels of HPCs. Plasma concentrations of analyzed OH-PCBs/PBDEs ranged from 0.1 to 100 nM in humans and up to 240, 454, 800, and 7650 nM for birds, fish, cetaceans, and other mammals, respectively. These concentrations fully fall within the *in vitro* effect concentrations reported in literature for HPCs of 0.05−10000 nM. We strongly advise further study of HPC blood levels in the general population, children, and fetal tissue to establish background levels and the risk at sensitive development stages. As not all HPCs are, or can be, chemically analyzed, the application of additional bioanalysis might reveal an even greater toxicological relevance of HPCs. In addition, metabolic activation should always be included within *in vitro* hazard assessment of POPs.



INTRODUCTION

Persistent organic pollutants (POPs) such as polychlorobiphenyls (PCBs) and polybromodiphenyl-ethers (PBDEs) are widely distributed in biotic and abiotic compartments, but a reduction or a leveling in biota has been observed during recent years.[1] However, contaminated environmental compartments such as soils and sediments serve as storage and act as "secondary sources".[2] These POPs are accumulated by the organisms, magnified through the food chain,[3] and can be transformed into hydroxylated- (OH- containing) metabolites.[4−6] Monitoring and effects analysis of POPs is mostly focused on the parent compounds, for which standards and analytical techniques are widely available, extraction procedures are relatively straightforward to apply, and environmental concentrations are higher compared to OH-PCBs/PBDEs and other halogenated phenolic compounds (HPCs). However, effects of PCBs and PBDEs in the endocrine and neuronal systems have been attributed to the action of their OH-metabolites.[7−9]

Chlorinated and brominated HPCs are usually reported and analyzed in separate publications. Among HPCs, OH-PCBs and 4-hydroxy-heptachlorostyrene (4OH-HpCs) are believed to be metabolites from anthropogenic PCBs and octachlorostyrene, respectively.[10,11] OH-PBDEs and bromophenols (BPhs) are naturally present in the marine environment[12−14] or they could be metabolites of PBDEs.[15,16] A number of tri-BPhs are commercially produced as flame retardants and wood preservatives.[17] Pentachlorophenol (PCP) was used as a wood preservative but is also a metabolite from hexachlorobenzene (HCB).[18] These HPCs have been detected and quantified in blood from humans, other mammals, birds, and fish.[11,19−21]

The basis for the retention of HPCs is their structural resemblance with the thyroid hormones (THs) 3,3′,5,5′-tetraiodo-L-thyroxin (thyroxine, T_4) and 3,3′,5-triiodo-L-thyronine (T_3).[22] Therefore, HPCs with the hydroxyl group in the para or meta position with one, but preferably two, halogens in the adjacent position[23] bind with high affinity to thyroid-hormone-binding proteins (THBP) such as transthyretin (TTR), thyroxin-binding globulin (TGB), and albumin (ALB).[24,25] This protects them from phase II metabolism and excretion, by retaining them in blood and facilitating their transport over selective barriers to the brain or the fetus.[26,27]

The competition of HPCs with thyroid hormones (THs) for the available transport proteins may cause direct effects on

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thyroid hormone homeostasis[28] but more importantly it allows delivery of HPCs instead of hormones to tissues,[29] including endocrine targets[30,31] and the neuronal system.[7] In fact, endocrine, developmental, and behavioral effects were observed upon direct exposure to 4-OH-CB107.[32]

Three recent publications from 2000, 2005, and 2010 have thoroughly reviewed the concentrations of various HPCs in wildlife.[1,5,33] To our knowledge, there is no comparable analysis available for human populations. In addition, observed concentrations of HPCs either in humans or in wildlife have not been compared with relevant toxicological information. Considering the increasing evidence of HPC toxicity, it is of great relevance to review the reported concentrations in relation to their observed effects. The aim of this meta-analysis is to review reported tissue-specific HPC body burdens of humans and wildlife species, to analyze their concentration in relation to their putative parent compounds, and to relate them to relevant toxicological threshold concentrations. This will allow a more realistic assessment of the potential hazard of this class of compounds and the relevance of metabolic activation of POPs.

METHODS

Literature Search. Keywords from the references cited by a recent POP exposure review[1] were used in a scientific bibliographic search through the databases Scopus (Elsevier B.V.) and PubMed (NCBI). The keywords were classified into four categories: parent compounds (e.g., PCB or "polychlorinated biphenyls"), chemical group (e.g., metabolites or hydroxylated), biological compartment (e.g., tissue or blood), and endpoint (e.g., effect or level). From the reference and citation list from each retrieved publication, relevant publications were also collected.

Selection Criteria. Papers with reported OH-PCB and/or OH-PBDE concentrations in tissues, published in peer-reviewed journals in English up to 2012 were included. Reports for PCP, tri-BPhs OH-HpCs, and TBBPA were only included in the analysis if OH-PCBs and/or OH-PBDEs were also reported. For separate publications reporting the same population and same sampling campaign, the first publication from the group or that one in which the data had been described with the highest level of detail was chosen for the database.

Collected Data. The following information was tabulated from each publication when reported: bibliographic data, subject or population data (species, gender, age, year, region, exposure level, and number of individuals), % lipid content, individual concentrations of most abundant congeners, as well as lowest, average (arithmetic or geometric mean, or median), and highest reported sums of congeners from PCBs, PBDEs, OH-PCBs, OH-PBDEs, PCP, tri-TBPhs, and OH-HpCs (database accessible through the WUR library E-depot: http://edepot.wur.nl/257263, excel file available upon request to the corresponding author). From each publication more than one entry could result depending of the number of species, tissues, or conditions reported.

Analysis and Calculations. Concentrations were harmonized to ng/g wet weight (ng/g ww) for all tissues. When the % of lipid was not reported, an average value from similar publications was used. Plasma, serum, and whole blood were all considered as blood and its density was set at 1 g/mL. Blood concentrations of HPCs were transformed into nanomol/liter (nM) units to allow comparison with *in vitro* toxicity data. The average molecular weights from the collected congeners used to calculate the nM values were 378.8 for OH-PCBs and 500.9 for OH-PBDEs. Exact molecular weights were used for PCP (266.4), 4-OH-HpCs (361.5), and tri-BPhs (330.7). The uncertainty of these calculations could lead to up to 80% variation, which is however below the data dispersion within reports. To reduce uncertainty from differences in sample composition and detection capabilities, results from the lowest, average, and highest reported values were combined in boxplots to show the tissue concentrations and variability in humans and wildlife. Graphs and regressions were made in SigmaPlot (SPSS).

RESULTS AND DISCUSSION

In total, 75 publications met the inclusion criteria to be in the database. Four studies with experimentally exposed animals were included in the database because they give insight into the mechanism of retaining and effects of metabolites, but not into the quantitative analysis of naturally exposed animals and humans. As a result, 211 entries were included in the quantitative analysis (Table 1). Although a reduction in OH-PCBs has been observed through the past decade (data not shown), reports before 2004 surveyed especially contaminated populations, whereas recent studies reported mainly on general populations, confounding a potential temporal analysis and perhaps influencing the overall results toward higher burdens.

Table 1. References of HPCs in Human and Wildlife Tissues Discriminated by Species Group and Tissue

species group	tissue	no entries[a]	sum of individuals[b]	references
Humans	Placenta/Umbilical Cord	1/2	17/39	36−38
	Liver/Milk/Adipose	1/2/3	5/23/76	37, 39−42
	Blood	62	2553	10, 11, 20, 37, 40, 42−55, 55−64
Birds	Eggs	15	172	65−68
	Liver	6	45	69, 70
	Blood	23	262	21, 52, 70−76
Fish	Fat[c]/Eggs	1/1	8/15	77
	Liver/Muscle	2/2	18/15	77−79
	Blood	22	70	19, 80−82
Cetaceans	Blubber/Liver/Milk	4/3/1	64/34/8	3, 83, 84
	Brain	6	21	85, 86
	Blood	24	253	3, 83, 87−92
Other mammals	Fat[c]/Brain/blubber	2/2/1	50/22/1	34, 35, 93
	Liver	4	34	34, 94
	Blood	20	283	10, 11, 21, 28, 34, 52, 91, 93, 95−97
	Laboratory exposed animals			
Mammals: rat, sheep, dogs and mouse	Various tissues, mainly blood	2/2/3	4/16/14	10, 15, 98, 99

[a]An entry is the report of HPCs (OH-PCBs and OH-PBDEs, and PCP, OH-HpCs and tri-BrPhs when included) in a given species and a give tissue. [b]Total number of individuals for the given entries (sum of n). [c]Adipose tissue.

In addition to the HPCs included in the analysis, data for hydroxyl-polybromobiphenyls (OH-PBBs) have been reported in polar bear adipose, brain, and liver, and ringed seal blubber at

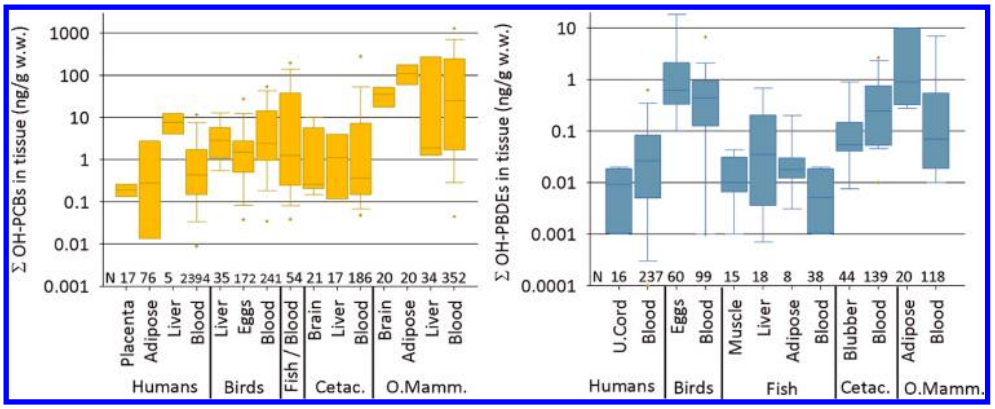

Figure 1. Distribution of the lowest, average, and highest reported concentrations of (A) OH-PCB and (B) OH-PBDE human and wildlife tissues including blood. Boxplots include data from the highest, average, and lowest sums of congeners reported in every entry for a range of tissues from humans and animals discriminated by species groups. Cetac. (cetaceans) and O.Mam. (other mammals). Values below boxplots indicate the number of all individuals included. Note the different scales.

similar or even higher concentrations compared with OH-PBDEs.[34,35] However, OH-PBBs seem to have a preference for adipose tissue retention[34] and their potency to bind THBPs is yet to be investigated.

Species and Tissue Concentrations of OH-PCBs and OH-PBDEs. Reported human and wildlife tissue concentrations were, in general, 10 to 100 fold higher for OH-PCBs (Figure 1A) compared to OH-PBDEs (Figure 1B). Blood and highly perfused tissues such as liver and brain contained higher OH-PCBs/PBDEs compared with muscle, blubber, and adipose tissue (Figure 1). Levels in tissues and body compartments with few entries such as human milk and umbilical cord; fish eggs; cetacean cerebrospinal fluid, milk, and liver; and polar bear brain and liver are listed in the Supporting Information but were not used in the analysis.

Studied human populations were mainly from North America, Japan and Europe with a few exceptions from Nicaragua and India. Human OH-PCB/PBDE concentrations in tissues were the lowest among species. Values of OH-PCBs in plasma from human males were considerably higher compared to those for mixed population and females (Supporting Information, Figure SF1). Higher OH-PCBs also have been observed in male dolphin plasma.[87] Although the authors attribute this to higher CYP activity induced by elevated PCB burdens, lower levels in females could also be the result of maternal transfer to offspring via lactation and deposition in eggs.[66,67]

Only six publications reported HPCs in fish and included mainly trouts, carps, and amberjacks whereas sharks and tuna seem to be the only marine species so far surveyed.[78,79,81,100] Given their allegedly lower metabolic activity, reported OH-PCBs in fish plasma range up to 100 ng/g ww. These might also demonstrate a lower phase II metabolic activity. However, these values are highly influenced by two reports from Detroit River fish[19,80] while others reported concentrations up to 0.4 ng/g ww in fish blood from the Great Lakes and Japan.[81,82]

Reported data in birds included, among others, gulls, falcons, eagles, and albatrosses. The concentrations of OH-PBDEs in bird eggs were remarkably high, averaging around 1 ng/g ww, which was double compared to reports of levels in blood (Figure 1B). Similar patterns of OH-PCBs and OH-PBDEs in bird blood and eggs[65] and their presence before embryonic development[68] strongly indicate their maternal transfer, but interspecies differences remain to be studied.[66] Furthermore, opposite to OH-PCBs, OH-PBDEs concentrations in birds are higher compared to fish, similar to cetaceans and to other mammals.

In the category of other mammals, mainly seals and polar bears plus a few reports on cats and dogs were found. They were the highest among the species, while these results are strongly influenced by very high polar bear levels. Even after removing one outlier entry,[34] polar bear blood was still up to 267 ng OH-PCBs/g ww.

Developments on Congener Analysis. Organic synthesis development and resources available to researchers influenced the number and type of congeners reported on publications. A number of 31−56 OH-PCB congeners, mainly tetra to nona chlorinated, were synthesized and identified in human and wildlife plasma between 1994 and 2002.[10,101] From the available standards, approximately 11−18 congeners were reported in literature until 2009. The most abundant reported congeners in humans and wildlife were: 4-OH CB 107, 3-OH CB 153, 3′-OH CB 138, 4-OH CB 146, and 4-OH CB 187, although the congener profile varies within species and locations. Analysis in birds and fish revealed also the importance of 4-OH CB 120, 4-OH CB 199, and 4-OH CB 202.[74,80] In 2006, 80% of the OH-PCBs in bottlenose dolphins (*Trupsiops truncatus*) from the Atlantic were still unidentified congeners,[87] whereas in 2009, 40% of measurable OH-PCBs identified in sharks, cetaceans and mammals were mono to tetra congeners.[52,81,89] Some of these contributing congeners have been identified as: 4′-OH CB 25/26/31, 2′-OH CB 61, 4-OH CB 61, 3-OH CB 66, 4-OH CB69, and 4-OH CB 79. Lower halogenated congeners structurally resemble closer T_3 than T_4, which may result in lower binding affinity to plasma THBPs, but reports of this group of congeners in humans is still lacking and the collected data in wildlife populations is insufficient to analyze the potential hazard implications.

Lower[102,103] and higher[104,105] brominated OH-PBDE have meanwhile been synthesized and identified in humans and wildlife. The most abundant congeners, 4′-OH BDE 17, 2-OH BDE 68, 4-OH BDE 42, 3-OH BDE 47, 6-OH BDE 47, 4′-OH BDE 49, and 4-OH BDE 92, have remained the same up to date and therefore big uncertainties are not to be expected.

There is still a large proportion of unidentified congeners, particularly OH-PCBs. From the potential 209 PCB and 209 PBDE congeners, only 62 PCB and 12 BDE congeners have been consistently reported to be present in human and wildlife

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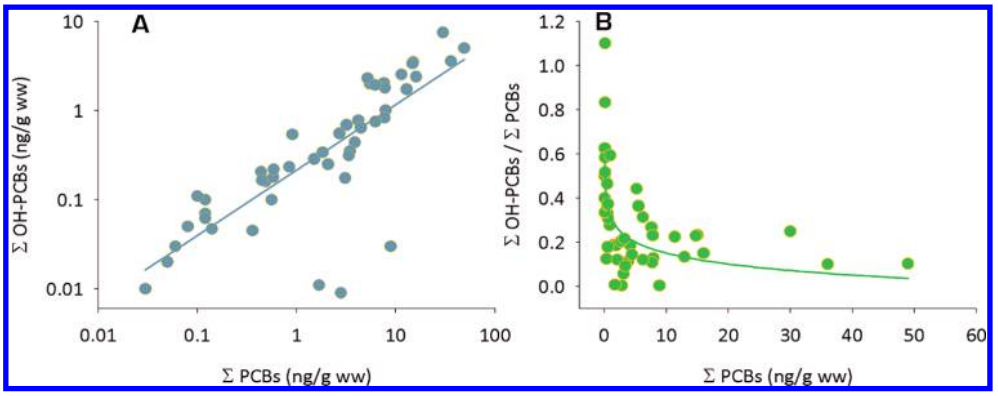

Figure 2. Correlation between absolute or relative metabolite concentrations and parent compounds for PCBs in human blood. Circles represent the average sum of congeners reported from each human entry. The (A) linear regression between ∑PCBs and ∑OH-PCBs ($y = 0.21 + 0.14*x$) and (B) logarithmic regression between ∑PCBs and the parent to metabolite ratios ($y = 0.31-0.072*\log_{10}[x]$) were both highly significant, $P < 0.0001$.

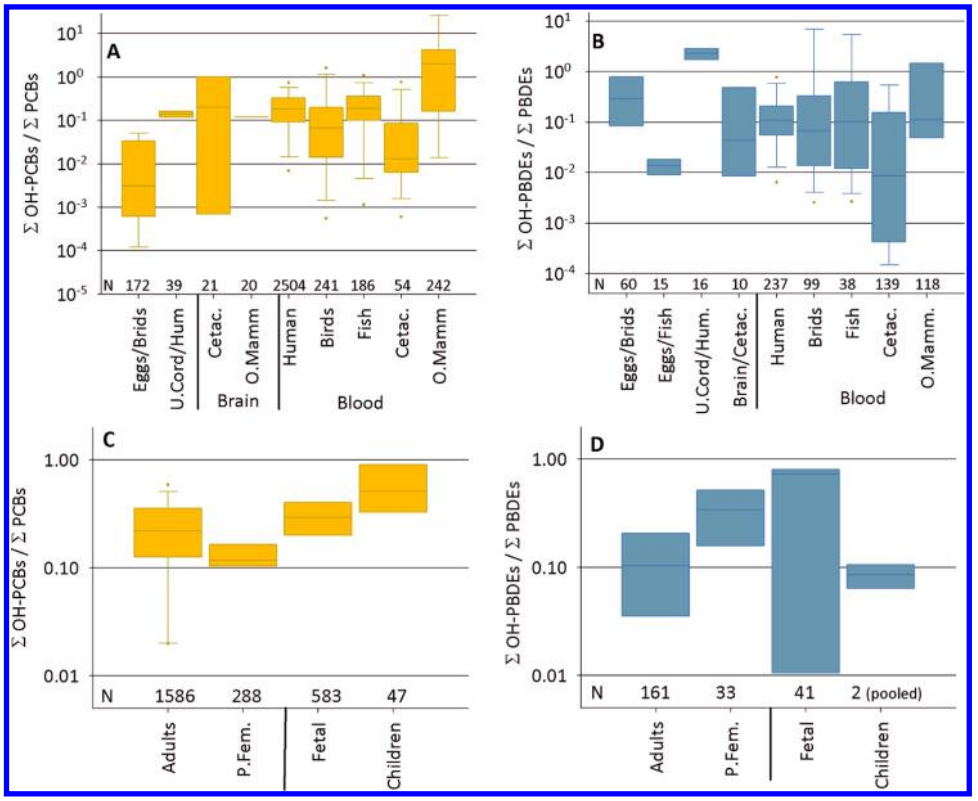

Figure 3. Ratio of ∑OH-PCBs/-PBDEs to ∑PCBs/PBDEs (A and B) in tissues of various species and (C and D) in human blood. Boxplots represent the distribution of the ratio from the average sums of (A and C) OH-PCB and (B and D) OH-PBDE congeners to the sum of their respective parent compounds. U.Cord. (umbilical cord tissue), Hum. (Humans), Cetac. (cetaceans), O.Mam. (other mammals) and P.Fem. (pregnant females). Values below boxplots indicate the number of all individuals included.

tissues. Several OH-metabolites may be produced from each of these parent compunds.[6,15,16,106] Considering the production of 4−6 metabolites per parent compound, the total number of metabolites could rise up to 400 congeners. Not all of these metabolites will be selectively retained in the blood and transported over placental and blood−brain barriers; however, this demonstrates the potential extent and complexity of an issue that clearly deserves further studies.

Relationship to Parent Compounds. Although a relative large number of OH-PCB congeners have not been analyzed, their levels in human blood significantly correlated with that of parent PCBs ($P < 0.0001$, Figure 2A) in agreement with previous results.[55] This correlation is less evident for blood concentrations in other species and for other tissues such as eggs or liver. The ratio of ∑OH-PCBs to ∑PCBs was highest in human blood at low PCB burdens (Figure 2B). At concentrations above 10 ng ∑PCBs/g w.w. the ratio was stable at 0.2 (approximately 5 nM ∑OH-PCBs). This stabilization could be the result of equilibrium between phase I and phase II metabolism and the THBP carrying capacity. However, several human and wildlife studies comparing control and contaminated populations found considerably higher metabolite to parent ratios on individuals with higher POP burdens.[20,51,63,97] Furthermore, rats and sheep exposed to PCBs had up to 17 times more OH-PCB than PCB in blood at the end of the exposure period.[10,98] Therefore, it is plausible to

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suggest that at higher PCB burdens, phase II metabolism cannot completely counterbalance the production of metabolites, and also the THBPs can transport much higher quantities of metabolites when required.

The metabolite/parent ratios are important indicators of the balance between production, retention and excretion of metabolites, as are important to establish potential source relationships. The ∑OH-PCBs/∑PCBs were high in blood, brain, umbilical cord and eggs (Figure 3A), which is in agreement with a higher burden of OH-PCBs in highly perfused tissues and active transport through selective barriers.[26] Children have more than twice as high ∑OH-PCB/∑PCB ratios than adults (Figure 3C). This result may be influenced by studies of particularly exposed populations.[47,63] The ratios reported in literature and discussed here probably represent an underestimation, particularly on OH-PCBs reports before 2010 as discussed earlier.

The tissues with the highest ∑OH-PBDE/∑PBDE are blood, brain and especially fetal tissue like eggs and umbilical cord (Figure 3B and D). These results therefore confirm an important transfer of OH-PBDEs into fetal tissues and suggest higher transfer efficiencies compared to OH-PCBs. For coastal and marine populations the main source of OH-PBDEs might not be metabolism of PBDEs but direct uptake of mainly ortho OH-PBDEs (Figure 4) directly from marine sources.[107] This

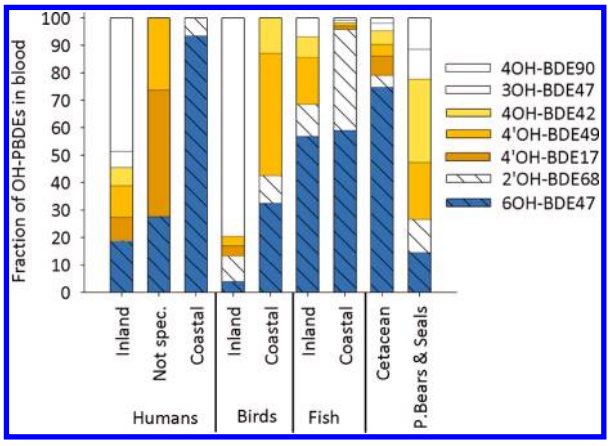

Figure 4. Relative presence of OH-PBDE congeners in blood, calculated based on the reported ng/g ww average levels per species group, distinguishing inland and coastal populations.

can explain the absence of correlation between ∑OH-PBDEs and the ∑PBDEs. In blood from inland populations, mainly meta and para OH-BDE congeners were present (Figure 4), supporting existing evidence toward metabolism from parent BDEs as their source.[15,16,106]

HPC Plasma Retention. The increased concentration of HPCs in relation to their putative parent compounds mainly in plasma but also in other highly perfused tissues (Figure 2) has been explained on the basis of their structural resemblance to thyroid hormones and hence their binding to the THBPs.[9,22] The main purpose of the THBPs is to provide a multicomponent buffer system to assess the even distribution of THs through the body[108] which otherwise will permeate into cell membranes and disappear from the bloodstream.[109]

In general, HPCs competitively bind TTR with similar potency compared to T_4 (Supporting Information, Table ST1) whereas most of them have lower affinity than T_4 for TBG. However, as the affinity of TBG for T_4 is almost 3 orders of magnitude higher than that for TTR, similar concentrations of, for example, some OH-PBDEs will equally compete with T_4 for TTR as they will do for TBG. This indicates that TBG contributes as well to the HPCs retention in plasma. ALB demonstrated similar affinity for HPCs compared to THs;[25] however, the importance of ALB on HPC retention and transport is yet to be asserted.

The concentrations of thyroid binding proteins vary among species and within stages of development (Supporting Information, Table ST2). In combination with their binding affinity, it is estimated that in humans TBG, TTR, and ALB carry 65%, 15%, and 20% of the bound T_4, and that one in three TBG molecules, one in 300 TTR molecules, and one in 3000 ALB molecules carry one T_4 molecule bound to it under physiological conditions. Therefore, about 100 nM of proteins have bound-T_4, and at least 200 nM of TGB and 4000 nM of TTR are available so a large amount of HPCs can be bound without direct competition with THs. This might explain the absence of consistent correlations between plasma HPC and TH concentrations.[110] Instead, the THBPs deliver the HPCs to the tissues where they can exert direct effects and/or interfere with TH sensitive processes altering feedback balances and hence TH homeostasis.[111,112] It is therefore important to consider the HPC burdens in perspective of their various mechanisms of toxicity.

HPC Burdens in Relation to Effect Levels. Besides OH-PCBs and OH-PBDEs, 4OH-HpCs and halogenated phenols such as PCP, TBBPA, and triBPhs bind to the THBP (Supporting Information, Table ST1). PCP was the major HPC found in human blood, whereas for all other species OH-PCBs were the most abundant HPCs (Figure 5). Birds had

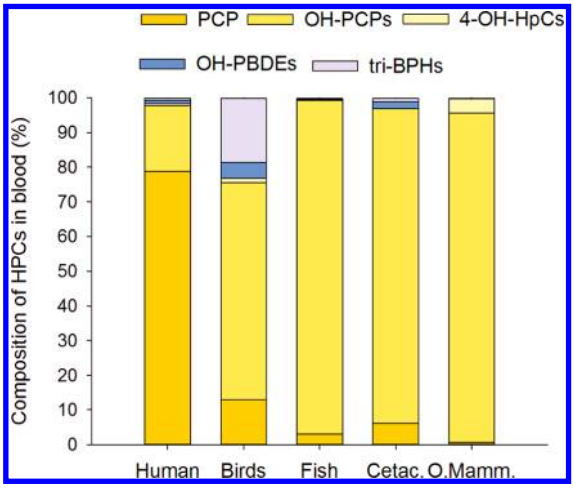

Figure 5. Composition of HPC chemical groups in blood. The composition is based on the average ∑HPCs per chemical group for all entries per species group, expressed in nM as explained in the Methods section.

relatively higher HPC levels, probably due to the fact that most publications reported on piscivorous coastal bird populations characterized by a major exposure to tri-BPhs and OH-PBDEs from marine sources (Figure 5).

This study aims at comparing the HPC body burdens of humans and wildlife to known effect concentrations. To this end, all reported concentrations were expressed in molar units, allowing sensible combination of relatively heavy brominated with also much lighter HPCs. The range of HPC concen-

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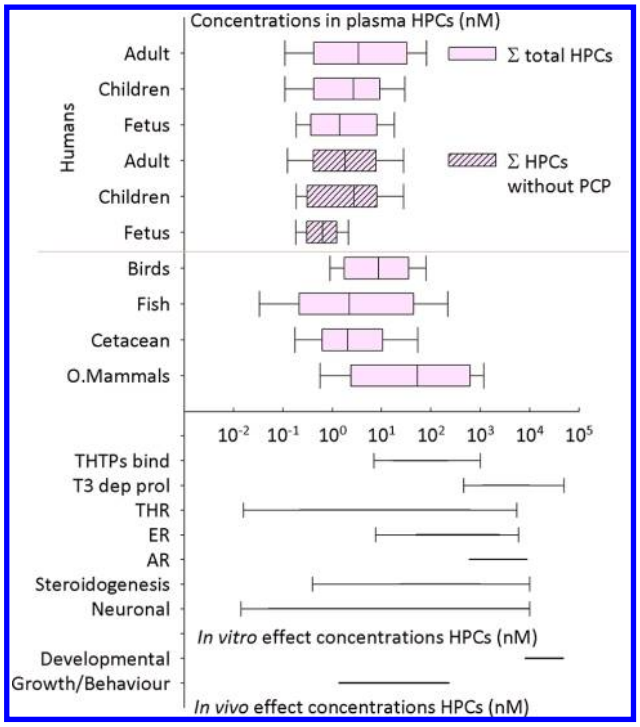

Figure 6. HPC concentrations in plasma from humans and wildlife compared to *in vitro* and *in vivo* effect concentrations. HPCs included reports from OH-PCBs and OH-PBDEs and also PCP, OH-HpCs, tri-BrPhs, and TBBPA when included. Boxplots represent the distribution of highest, average and lowest sums of congeners in blood from humans and animals (nM) calculated from values reported in the literature included in this study. Cross-hatched boxes indicate human HPC concentrations without PCP. Lines indicate *in vitro* effect concentrations (nM) for THBP binding, T-screen, thyroid hormone (TH)R, estrogen (E)R and androgen (A)R receptor activation, steroidogenesis, neuronal outgrowth, and in vivo effect concentrations for mammalian growth and development. Details and references can be found in Supporting Information, Table ST3.

trations in human blood was 0.1−100 nM including PCP and 0.2−20 nM without PCP (Figure 6). The total HPC range in human blood is one fold higher when PCP concentrations are included. Highest reported PCP values were 187 nM in blood from Swedish men.[59] But it seems that PCP concentrations have decreased in recent years to levels below 40 nM (approximately 10 ng/mL).[113] The results reveal that children and fetal cord blood HPC concentrations are similar to those in adults (Figure 6). HPC concentrations in wildlife plasma were in the range of 1−240 nM in birds, 0.2−454 nM in fish, 0.1−800 nM in cetaceans, and were highest (0.05−7650 nM) in other mammals (Figure 6); while as mentioned before, still not all OH-PCBs have been quantified.

Among the relevant *in vitro* end-points (references in Supporting Information, Table ST3), thyroid hormone competitive binding has been most widely studied. THBP competition is observed from 5 to 1000 nM, whereas a higher quantity (200−50000 nM) is generally required to trigger T_3 dependent proliferative effects in the T-screen (Figure 6). Effects of HPCs on nuclear receptors are structurally dependent and required concentrations above 5 nM to act as agonist or above 1000 nM as antagonist. However, activation of thyroid hormone receptor (THR) by HPCs has been observed already from 0.03 nM. HPCs inhibit aromatase and other steroidogenic enzyme activities from 500 nM, whereas gene expression in the same pathway is altered above 1000 nM. Neuronal effects on Ca^{2+} homeostasis and neurotransmitters have been observed above 200 nM; however, abnormal dendritic development is shown after exposure to OH-PCB concentrations as low as 0.005 nM.

Thyroid hormone homeostasis, estrogenic, behavioral, and neuronal effects were observed in offspring from pregnant rats exposed to 4-OH CB107.[26,32,114] Acute toxicity in adults, and various developmental effects in embryos were observed on zebrafish exposed to 6-OH BDE 47, while liver concentrations were 170−940 nM and 300 nM respectively.[115] Similar developmental arrest was obtained after zebra fish exposure to three OH-BDE congeners.[116] Finally, exposure to a combination of CB118 and CB153 during sheep gestation influenced fetal growth, adrenal development, cortisol production,[117] and offspring sexual dimorphic behavior.[118] In this case, 3−85 nM of 4-OH CB107 and 4-OH CB146 were found in plasma from the same lactating ewes 50 days after birth[98] (Figure 6). Only very few *in vivo* exposure studies with either OH-PCBs/PBDEs or parent compounds report plasma effect concentrations allowing comparison with OH-PCB/PBDE levels in humans and wildlife.

CONSLUSIONS, KNOWLEDGE GAPS AND PERSPECTIVES

Plasma HPC (OH-PCB, OH-PBDE, PCP, OH-HpCs, and tri-BPhs) concentrations reported ranged from 0.1 to 100 nM in humans and up to 240, 454, 800, and 7650 nM for birds, fish, cetaceans, and other mammals. Although still only a selection of HPCs can be and were analyzed, these concentrations are well within the range of observed *in vivo* and *in vitro* developmental, endocrine, and neuronal effects. Metabolic activation and the retention of OH-metabolites in plasma should be more explicitly considered within a more realistic hazard assessment of POPs, especially when this is based on *in vitro* analyses.

General population studies and the surveillance of a single population are required to determine background levels and temporal trends. These studies should especially pay attention to levels in fetuses (umbilical cord blood) and children as the scarce information present indicate relatively high concentrations of OH-PCBs and OH-PBDEs that are of concern. The results of fetal tissue analysis, including human cord blood and bird eggs, suggest a greater maternal transfer efficiency of OH-PBDEs compared to that of OH-PCBs, an important aspect of exposure that must be further investigated.

Arctic top predators hold HPCs concentrations comparable to total TH transport protein capacity. Studies on nonarctic top predators and other important piscivores and carnivores are warranted. Two studies reported OH-PCB or OH-PBDE plasma concentrations in pets.[52] These animals live in close association with house dust and lick their fur; they could serve as sentinel species to study indoor exposure of especially small children.

Biological methods should be developed to be able to include the toxic potencies of HPCs that cannot be chemically detected because standards do not (yet) exist or they occur in levels below the limit of detection; while they do contribute to the combined HPC risk. Retrospective studies applying those more comprehensive methods to stored samples (including blood plasma from *in vivo* experiments and umbilical cord) may reveal an even greater toxicological relevance of OH-PCBs/PBDEs than already indicated by the results of our current meta-analysis.

■ ASSOCIATED CONTENT

Supporting Information

Available Supporting Information includes: the list of individual congeners included in the database; the concentrations of HPCs not included in Figure 1; Figure S1 depicting the distribution of reported concentrations of OH-PCBs and OH-PBDEs in human plasma; Table ST1 with the summary of competitive binding parameters of hormones and HPCs to transport proteins; Table ST2 with the levels of hormone carrying proteins and thyroid hormones in various species and Table ST3 with the sources of information for the *in vitro* effect concentrations displayed in the Figure 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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