HHS Public Access

Author manuscript

J Hazard Mater. Author manuscript; available in PMC 2023 March 15.

Published in final edited form as:

J Hazard Mater. 2022 March 15; 426: 128084. doi:10.1016/j.jhazmat.2021.128084.

The aryl hydrocarbon receptor: a predominant mediator for the toxicity of emerging dioxin-like compounds

Wanglong Zhang[1], **Heidi Qunhui Xie**[2,3], **Yunping Li**[2,3], **Mingxi Zhou**[4], **Zhiguang Zhou**[5], **Renjun Wang**[1], **Mark E. Hahn**[6,7], **Bin Zhao**[2,3,*]

[1]College of Life Sciences, Qufu Normal University, Qufu, Shandong 273165, China

[2]State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China

[3]University of Chinese Academy of Sciences, Beijing 100049, China

[4]Biology Centre of the Czech Academy of Sciences v.v.i, Institute of Plant Molecular Biology, Branišovská 31, 370 05 České Budějovice, Czech Republic

[5]State Environmental Protection Key Laboratory of Dioxin Pollution Control, National Research Center for Environmental Analysis and Measurement, Beijing 100029, China

[6]Biology Department, Woods Hole Oceanographic Institution (WHOI), Woods Hole, MA 02543, USA

[7]Boston University Superfund Research Program, Boston University, Boston, MA 02118, USA

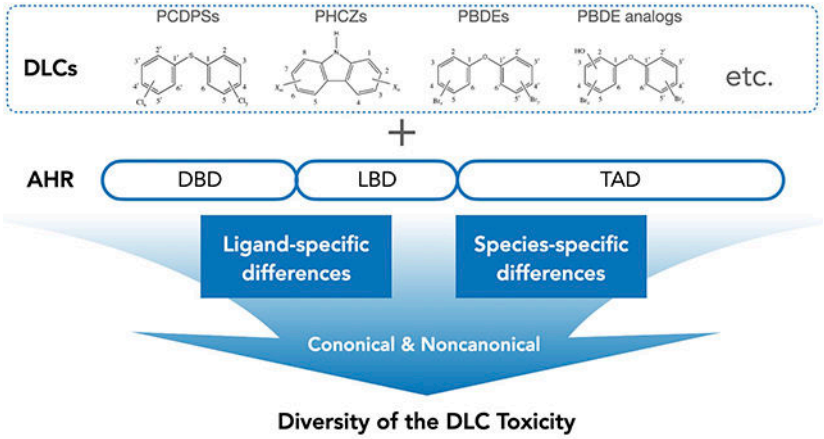
Abstract

The aryl hydrocarbon receptor (AHR) is a member of the basic helix-loop-helix/Per-ARNT-Sim (bHLH-PAS) family of transcription factors and has broad biological functions. Early after the identification of the AHR, most studies focused on its roles in regulating the expression of drug-metabolizing enzymes and mediating the toxicity of dioxins and dioxin-like compounds (DLCs). Currently, more diverse functions of AHR have been identified, indicating that AHR is not just a dioxin receptor. Dioxins and DLCs occur ubiquitously and have diverse health/ecological risks. Additional research is required to identify both shared and compound-specific mechanisms, especially for emerging DLCs such as polyhalogenated carbazoles (PHCZs), polychlorinated diphenyl sulfides (PCDPSs), and others, of which only a few investigations have been performed at present. Many of the toxic effects of emerging DLCs were observed to be predominantly mediated by the AHR because of their structural similarity as dioxins, and the *in vitro* TCDD-relative potencies of certain emerging DLC congeners are comparable to or even greater than the WHO-TEFs of OctaCDD, OctaCDF, and most coplanar PCBs. Due to the close relationship between AHR biology and environmental science, this review begins by providing novel insights into AHR signaling (canonical and non-canonical), AHR's biochemical properties (AHR structure, AHR-ligand interaction, AHR-DNA binding), and the variations during AHR transactivation. Then, AHR ligand classification and the corresponding mechanisms are discussed, especially

*Address correspondence to Dr. Bin Zhao, Research Center for Eco-Environmental Sciences (RCEES), Chinese Academy of Sciences, Beijing 100085, China; Telephone: (86) 010-62842867; binzhao@rcees.ac.cn.

the shared and compound-specific, AHR-mediated effects and mechanisms of emerging DLCs. Accordingly, a series of *in vivo* and *in vitro* toxicity evaluation methods based on the AHR signaling pathway are reviewed. In light of current advances, future research on traditional and emerging DLCs will enhance our understanding of their mechanisms, toxicity, potency, and ecological impacts.

Graphic Abstract



Keywords

aryl hydrocarbon receptor; AHR ligands; dioxin-like compounds; molecular mechanisms; toxicity evaluation

1. Introduction

The aryl hydrocarbon receptor (AHR, also called dioxin receptor), a member of the basic helix-loop-helix/Per-ARNT-Sim (bHLH-PAS) family of transcription factors, was identified more than four decades ago and is well known for its ability to mediate a series of biological and toxic effects caused by environmental contaminants, including polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/Fs) and many other halogenated aromatic hydrocarbons (HAHs), often referred to as 'dioxin-like compounds (DLCs)' [1–3]. These compounds occur ubiquitously in various environmental matrices, and many of them undergo bioaccumulation and biomagnification [4–6]. The toxicity of PCDD/Fs and dioxin-like polychlorinated biphenyls (DL-PCBs) has been extensively investigated, but our understanding remains incomplete, with many adverse effects being continuously revealed [7–9]. A variety of emerging DLCs such as polyhalogenated carbazoles (PHCZs) and polychlorinated diphenyl sulfides (PCDPSs) are being found to act by a similar mechanism to dioxins via AHR, but there are many compound-specific effects and detailed mechanisms remain largely unknown. Research on human samples has indicated the occurrence of emerging DLCs and has suggested their potential risk to human health [10–12]. Due to DLCs' adverse effects like that of the dioxins, and the importance of AHR as a key mediator, much research has been performed to evaluate their toxicity and obtain preliminary mechanistic knowledge [13, 14]. Indeed, the understanding of DLC toxicity largely depends on the current

knowledge of AHR biology; thus, advances in AHR biology (e.g., structural insights into AHR-DNA binding or detailed transactivation mechanisms [15, 16]) would benefit future research on DLC-AHR interactions and their downstream effects.

It is now widely accepted that AHR has broad functions, including playing roles in human physiology (e.g., development biology, neurobiology, and immunology), diseases (e.g., autoimmune diseases and cancer), and chemical toxicity [17–20]. Beyond these cellular and physiological aspects, the AHR gene and its functions in most metazoans have both conserved and varied roles, and further study of AHR can enhance the understanding of the toxicology of AHR-active contaminants in distinct species [21]. Organisms in certain areas may suffer from exposure to a particular dioxin/DLC and its potential adverse effects in a species-specific manner, so the role of AHR in different species should be carefully evaluated, including the number of homologs, expression level, predominant form, and AHR sensitivity [22–24]. Moreover, AHR can be used by environmental scientists as a tool in toxicology research based on ligand-induced AHR activation, with species-specific effects being considered [25], such as for developing bioassays for evaluating toxicity or identifying novel ligands/contaminants [26, 27].

Since knowledge of AHR biology is rapidly growing, further advances could improve many aspects of environmental science, such as contaminant quantification/screening, toxicity evaluation, species-specific effects, and mechanistic exploration. Recent biochemical and structural research has provided increasing evidence that the physicochemical features of ligands, structural determinants of AHR, and interactions of AHR and ligands could influence its transactivation process (and sometimes its toxic potential) [15, 28–30]. To provide information for more thorough DLC toxicology research, this review describes recent advances in research on traditional and emerging DLCs by focusing on (*i*) advances in understanding of the AHR transactivation process (e.g., AHR-ligand interactions, AHR-DNA binding, and nongenomic mechanisms); (*ii*) variations or uncertainty during the transactivation process (e.g., ligand-specific effects and species-specific effects); (*iii*) AHR ligands, especially emerging toxic DLCs, and their mechanisms; and (*iv*) toxicity evaluation assays for potential ligands/DLCs.

2. The AHR pathway

AHR is a nuclear receptor belonging to the bHLH-PAS family and is present in most metazoans. AHR has an evolutionary history of at least 600 million years [1]. Vertebrate AHRs are the most well characterized AHRs and were initially believed to sense exogenous molecules, but currently, research has widened the knowledge of the functions of AHR, such as governing many cellular/physiological functions and playing a role in human disease [17–20]. *Caenorhabditis elegans*, a modern representative of an early-diverging metazoan, has a “protoAHR” [1] that does not bind well-known AHR ligands such as TCDD and BNF [31, 32] (and may be constitutively active), but maintains some fundamental roles of AHR in neuronal differentiation and migration, and cell fate determination [33]. However, at an unknown time, ancient AHR acquired the ability to bind and be activated by many internal and external ligands, especially the high-affinity ligand TCDD and some halogenated aromatic hydrocarbons (HAHs) [1]. Thus, the AHR may have evolutionarily conserved,

fundamental biological roles in all animals, as well as species-specific properties. In more recently diverged animals such as vertebrates, the multitasking feature of AHR can be attributed to two major types of molecular mechanisms in cells, the canonical genomic pathway and non-canonical pathways [34, 35].

2.1 Canonical genomic pathway

AHR is a ligand-dependent nuclear receptor (Figure 1); when absent from ligands, it is maintained in an inactive form and protected from degradation by complexing with chaperones, including HSP90, p23, and XAP2 (also called Ara9 and AIP) [36]. At this stage, certain functional sequences and interfaces of AHR (e.g., the nuclear localization sequence (NLS) and ARNT dimerization interface) are blocked, ensuring that AHR is localized in the cytosol [15]. Once bound with an agonist ligand, AHR subsequently undergoes a structural transformation and translocates to the nucleus to dimerize with ARNT and bind specific DNA recognition sites with high affinity [15]. The DNA binding sites can be consensus or non-consensus sequences (see Section 2.2). The consensus site is a 5'-GCGTG-3' core motif usually named the dioxin response element (DRE) or xenobiotic response element (XRE). Then, the dimer recruits the basal transcription machinery to transcribe its target genes to exert various downstream functions (Figure 1).

As an important part of transactivation, the detailed AHR-DNA binding mechanism was revealed by resolving the structure of the core AHR-ARNT-DRE complex, which illuminated the principal role of the bHLH domain of both AHR and ARNT in recognizing the DRE, as well as the key interface for AHR:ARNT dimerization [16]. In addition, the two PAS domains have been shown to have distinct functions. The PAS-A domain is involved in ARNT dimerization [16, 36]. The PAS-B domain is part of the ligand-binding domain (LBD) of AHR and facilitates interactions with HSP90 or other cofactors, such as pRb [37, 38]. As the 3D crystal/NMR structure of LBD has not been characterized, which hampers the detailed understanding of AHR-ligand binding [34], researchers have built homology models using available PAS domain structures as templates to provide insights into AHR-ligand interactions or for mechanistic exploration of many unidentified forms of AHR in distinct species [39–42]. In addition to the LBD, the diversity of transactivation domains (TADs) of AHRs of various species or strains could have a role in determining the AHR activity, as indicated by research on AHRs in the H/W rat and hamster [43, 44].

Presently, a more detailed structural exploration of AHR (and the AHR-partner complex) and the molecular dynamics of AHR have yet to be investigated. In environmental science, many emerging DLCs are able to activate the canonical pathway of AHR and induce the prototypical biomarkers CYP1A1 and CYP1B1 (Figure 1) [45]. Although the genomic pathway is canonical in mediating the toxic effects of contaminants (including emerging DLCs), it is noteworthy that even toxic-equivalent doses of ligands may induce rather different effects both *in vitro* and *in vivo*. The reason for these differences may lie in the metabolic liability of distinct ligands, their pharmacokinetic and distributional differences, and the variations in their induced non-canonical crosstalk [46, 47]. In particular, investigating non-canonical crosstalk would be a good strategy to explain these differences.

2.2 Non-canonical pathways

Non-canonical pathways of AHR action, including crosstalk of AHR with other proteins/pathways, are of increasing interest but are not well understood. Systems biology research has revealed the ligand-specific coregulation and coexpression patterns of AHR with other genes, indicating the potential of AHR to crosstalk with other proteins/pathways [48]. Non-canonical mechanisms of AHR action can be classified into several patterns (Figure 1): (*i*) AHR associates with other transcription factors and then binds to non-consensus DREs (e.g., RelB [49] and KLF6 [50]) or indirectly binds to the DNA binding site of the associated partner (e.g., ER [51] and E2F1 [52]); (*ii*) AHR directly binds some functional components, and they cooperatively exert a particular function, such as ubiquitin ligation [53]; and (*iii*) AHR interacts with various signaling pathways (e.g., JNK [54] and Src [55]). Collectively, in most cases of non-canonical signaling, AHR is more like a signaling mediator rather than a transcription factor, and ligand-dependent activation is also not always necessary [37].

Non-canonical mechanisms are environmentally relevant because they can contribute to the toxicity of contaminants, including DLCs [56, 57]. For example, it has been found that lipophilic chemicals from diesel exhaust particles, which contain polycyclic aromatic hydrocarbons (PAHs) and numerous unsolved compounds, can trigger calcium responses in human endothelial cells via AHR-dependent nongenomic signaling indicated by pharmacological inhibition and RNA interference [56]. As another example, the uremic toxin indoxyl sulfate (IS) can induce endothelial hyperpermeability via an AHR/Src-dependent pathway [58]. Currently, research on non-canonical crosstalk of AHR is largely focused on a limited number of crosstalk factors/pathways and their effects, especially of dioxins (especially TCDD), which should be extended to other AHR-active DLCs in light of the results of TCDD research.

3. Variation during AHR transactivation

The AHR transactivation has many steps that can be affected by ligands' physicochemical properties. In light of the structural and biochemical research on AHR, DLCs' specific toxicity potential and mechanistic variations can be partly explained, including but not limited to the following aspects.

3.1 Possible ligand-specific structural changes of AHR

During AHR activation, several transitional stages can affect the outcome [15, 34]. AHR activation by a ligand binding initiates a multi-step process of AHR transformation before the AHR:ARNT heterodimer binds to DNA. Although the precise processes are still elusive, recent research has proposed a potential mechanism and described several factors that may influence the transformation process and subsequent transactivation of target genes [15]. Between ligand binding and DNA recognition by AHR, there may be two major transitional steps, including 'step one' of switching HSP90 into an open form and exposing the AHR's NLS motif, followed by translocation of the AHR:HSP90 complex to the nucleus; 'step two' is the formation of a ternary complex of AHR:HSP90:ARNT before transforming into the competent state of the AHR:ARNT complex that can bind DNA [15]. Both steps are likely altered by the conformational change of PAS-B following ligand binding, which

may subsequently influence the efficiency of ARNT recruitment after ‘step one’ and HSP90 dissociation in ‘step two’ [15]. These steps are essential for AHR activation and may occur in a ligand-specific manner. There is evidence that binding of agonists and antagonists result in different AHR structures [59]. Moreover, the subsequent efficiency of AHR transformation and DRE binding can also be specifically influenced by binding distinct ligands [60]. This suggested that the varied effects of ligands may result from ligand-induced overall structural alterations of AHR or the AHR:ARNT heterodimer (or perhaps a heterodimer of AHR and other partners), therefore affecting subsequent DRE recognition and cofactor recruitment [34]. However, the true mechanism may involve one or several of the aspects discussed above. At present, there are still no direct observations of ligand-specific AHR structural changes, which therefore should continue to be investigated.

3.2 Variations during AHR-DNA recognition

In addition to AHR transformation, subsequent DNA binding is another influential process. A recent study on the AHR:ARNT:DRE structure has provided insights into the DRE recognition process and a new avenue to investigate the ligand-specific effects induced by different DRE binding efficiencies or priorities [16, 60]. As mentioned in Section 2.2, the DRE is an essential factor for AHR-DNA recognition. The classic binding mode is that AhR:ARNT heterodimer binds to a consensus DRE sequence (5’-GCGTG-3’) in the target gene promoter (Figure 1) [61, 62]. Genome-wide analysis of DREs indicates that most TCDD-inducible genes contain DREs within the 10 kb upstream or transcribed regions [63, 64]. Alternatively, other sequence(s) (e.g., XRE II) unlike the consensus DRE, can be recognized by AHR-interacting factors and govern the gene expression [65]. Here, the AHR acts more like a coactivator.

Initial evidence indicated ligand-specific DNA recognition by the AHR:ARNT heterodimer [66, 67], but later research has not confirmed these results using similar experimental models, suggesting that AHR likely does not utilize a ligand-specific DNA recognition mechanism in its signaling [68]. However, the efficacy of a particular ligand in stimulating AHR transformation/DNA binding can vary [69]. Indirubin, for example, has high efficacy/potency with the human AHR [60].

To explore the functional domain/region determining species differences in DRE binding by indirubin-activated AHR, swapping the LBD from a human AHR to a mouse AHR made the chimera more efficient at binding the DRE than the wild-type mouse AHR. However, the efficacy of indirubin with the chimera was also not the same as that with human AHR, which indicates that AHR regions outside of the LBD may have a role in ligand-specific DRE binding [60], as well as the importance of PAS-B conformational changes upon ligand binding for subsequent cofactor recruitment, DRE binding, and AHR activation. Therefore, for DLCs’ toxicity evaluation, DRE recognition or efficacy is vital to indicate their toxic potentials. But the DLCs-induced DRE binding now has not been much investigated, although some indirect evidence has revealed the DLCs’ DRE binding potential using DRE-driven reporter gene assays (i.e., polyhalogenated carbazoles) [14].

3.3 AHR pathway self-regulation

As a vital aspect of AHR pathway, its regulation or self-regulation (e.g., AHR, ARNT, AHR repressor (AHRR), and AHR target genes) by environmental contaminants have been frequently reported [70]. Regarding transcription, the biochemical state of AHR, ARNT, or CYP1A promoters plus their whole gene body could potentially influence their expression [71–73]. For instance, exposure to environmental contaminants exerts epigenetic regulation through the AHR promoter (i.e., histone modifications, such as the notably decreased trimethylation of histone 3, lysine 27) [70] or results in biochemical changes in the AHR protein as a feedback (e.g., ubiquitination and phosphorylation) [74, 75]. In addition to transient biochemical changes, in ecology, decades of exposure to PCBs causes selective pressure on certain regions of genes involved in the AHR pathway in wild species, thus having a long-term influence on their expression or function [22, 76–79].

Besides transcriptional or posttranslational regulation, feedback loop mechanisms are essential for cellular homeostasis (Figure 1) [80, 81]. One of the most potent patterns is the induction of the AHRR, which is a target gene of AHR [82, 83]. The AHRR can be sensitively upregulated (~150-fold induction) to exert robust suppression of AHR by forming a heterodimer with ARNT and competing with AHR-ARNT complexes for DRE binding, thus suppressing the canonical genomic response [30, 81]. More than competing for DRE occupancy, AHRR also inhibits DRE-mediated transcription by influencing the chromatin structure around the promoters of CYP1A1 and presumably those related DRE-driven genes [84, 85]. As another AHR target gene, TIPARP can ADP-ribosylate AHR and reduce its activity and half-life [86, 87].

Except for those genetic or epigenetic regulations, the modulation of the endogenous ligand FICZ can be another sort of regulation, as certain chemicals (e.g., quercetin, resveratrol, and curcumin) can repress CYP1-mediated degradation of endogenous FICZ, which can activate AHR in an indirect manner [88, 89]. Collectively, the AHR transactivation process is complex and during which multiple factors can independently or cooperatively cause variations. Especially, when investigating DLCs, the ligand- and species-specific effects through and on the AHR should be carefully considered.

4. Diversity of AHR ligands and ligand-specific effects

4.1 Overview of AHR ligands

In environmental science, evaluating the toxicity and exploring the molecular mechanism of AHR-active ligands, especially contaminants, are of great interest. AHR pathway signaling is an important theoretical basis for developing receptor-based toxicity evaluation systems for environmental pollutants. Multiple *in vitro*, *in vivo*, and *in silico* methods have been developed to identify potential AHR ligands (agonistic or antagonistic) [60, 90]. These natural or synthetic ligands can be classified into environmental contaminants (e.g., HAHs), marketed/prodrugs (e.g., rifampicin and rifabutin) [91], natural or endogenous metabolites/compounds [92, 93], industrial products (e.g., quinoline yellow dyes) [94], and others. Currently, the number of AHR ligands is increasing and their diverse mechanisms have been continuously identified. For instance, ligands with pharmaceutical effects, which are usually

termed selective AHR modulators, exert their function in a ligand-specific manner via AHR (e.g., for treating cancer or inflammation) [95–97]. Similarly, for environmental contaminants, ligand-specific effects should be of interest to environmental scientists or toxicologists and thus are also reviewed below.

A recent view has questioned the traditional classification of AHR ligands into ‘agonists’ or ‘antagonists’ and proposes that ‘modulator’ is a more appropriate term [98]. Some new terms have been adopted according to certain demands, including selective AHR modulators (sAHRMs) [97] and rapidly metabolized ligands (RMAHRLs) [99]. sAHRMs are compounds that bind and activate AHR and then regulate a selected pool of canonical and/or noncanonical target genes, therefore eliciting specific biological effects. Certain sAHRMs can exert beneficial functions without causing dioxin-like toxicity (e.g., 6-MCDF, 3,30-DIM) [98]. RMAHRLs (e.g., IMA-06201 and IMA-06504) are AHR agonists endowed with fast metabolic degradation, and they are devoid of dioxin-like toxicity due to the lack of their harmful bioaccumulation and the short half-life of the activated AHR complex [98]. RMAHRLs may be a subgroup of sAHRMs that have a highly polar physicochemical nature [98]. Currently, the definition of sAHRMs is still ambiguous [100]. The metabolic kinetics and the subsequent gene regulation may vary among ligands, including among the emerging DLCs, which are another important group of AHR ligands that have been ubiquitously identified in the environment (usually with persistent nature) and have received increasing focus due to their toxic potential. For instance, the emerging DLC 4,4’-di-CDPS has high bioaccumulation potential in mussel tissues and four metabolites were identified with the S-oxidation representing the dominant metabolic pathway [101]. However, with respect to metabolism, there is a need for further exploration of the detailed metabolic pathways (including variation among species [101, 102]) for all of the emerging DLCs. With respect to activity, most dioxins and DLCs have been found to have agonistic effects, while some also have partial or weak agonistic potential [103, 104].

4.2 Ligand-specific effects via AHR

Beyond those definitions, true ligand-specific effects should be considered. Numerous pieces of evidence have revealed the ligand-specific effects of AHR, and even when treated using compounds under the same TEQ, their outcome could be distinct from a systems biology or histopathology viewpoint [46]. The possible reasons may lie in the metabolic potential of distinct ligands, as traditional persistent HAHs can continuously activate AHR, while rapidly metabolized ligands (like the RMAHRLs discussed above) cannot [105, 106]. In line with this finding, Hoffman et al. has reported that persistent ligands tend to elicit great ultrasensitivity and the maximal response, while consumption-based ligands (e.g., indole-3-carbinol, an exogenous ligand identified in cruciferous vegetables, and its metabolite 3,3’-diindolylmethane) seem to produce low-level activation in a graded manner [107].

As a metabolically stable and potent compound, TCDD does not induce AHR to bind the stanniocalcin 2 (Stc2) promoter the same way it binds the CYP1A promoter [108]. In contrast, cinnabarinic acid (CA), a proposed endogenous agonist [109], cannot induce AHR to bind the CYP1A promoter [110]. Among PCB congeners, their intrinsic efficacies span a continuum between full agonism and full antagonism, and a weak agonistic congener yields

less than additive responses in mixtures with potent agonists [69]. Similarly, PCB-11 may act as a partial agonist/antagonist of AHR when co-exposed with the potent agonist PCB-126. However, PCB-11 does not block but exacerbates toxicity when co-exposed with BNF [103]. As another example, the full antagonist CH223191 blocks TCDD but has little inhibitory effect on BNF, PAHs, flavonoids, or indirubin [111].

Taken together, as the initial step, these variations were largely affected by the molecular initiation event (MIE), which mainly depends on the AHR-ligand interactions, of which the ligand binding pose and binding affinity are two of the major determinant aspects.

4.3 Ligand-binding affinity

Ligand-binding affinity is important for predicting the transactivation potential of AHR ligands for structurally similar classes of compounds. Competitive ligand-binding assays are commonly used methods for determining ligand-binding affinity. In a strictly restricted model with TCDD as the ligand to test a series of mutated forms of AHR, ligand-binding affinity shows good correlation with the following step of DNA binding (not transactivation activity) [15]. Among distinct ligands or forms of AHR, the situation is more complicated, and a stronger binding affinity does not ensure greater final activity (agonistic or antagonistic). Murray et al. has revealed similar competitive ligand binding profiles for α-NF (IC50 = 25 nM) and DiMNF (IC50 = 21 nM) but proposed that distinct agonist/antagonistic effects on DRE-mediated gene expression are unlikely to result from (or have a certain correlation with) the relative binding affinities [98, 112]. α-NF acts as a partial agonist that can induce CYP1A target gene expression and elicit DRE probe binding. However, DiMNF inhibits CYP1A expression and lacks DRE-binding capability. Further predictive docking modeling suggests that DiMNF adopts a unique orientation with higher binding energy within the AHR LBD as compared to α-NF, which may enable AHR binding but not subsequent DRE binding [112]. Accordingly, Some DLCs (i.e., certain PBDE congeners) do bind the AHR with low to moderate affinity but elicit non-detectable (or very weak) DRE binding [113].

5. Toxicity of emerging AHR-active contaminants

5.1 DLCs and toxic potency

It is now clear that a number of ligands can activate AHR but do not elicit dioxin-like toxic effects; therefore, agonists of AHR can be divided into ‘toxic’ and ‘nontoxic’ categories, whose effects need to be respectively discussed. Metabolically stable compounds (e.g., TCDD and many HAHs) induce toxic effects, likely attributed to the persistent or sustained activation of AHR, which also suggests the toxic potential of some emerging DLCs with a persistent nature [98, 114]. Among those toxic ligands, the production, distribution, transformation, and bioaccumulation of dioxins and DL-PCBs remain of great concern. Dioxins and DL-PCBs were included as initial persistent organic pollutants (POPs) in the Stockholm Convention on Persistent Organic Pollutants that need to be eliminated or their formation and release prevented. In 2005, certain congeners of dioxins and DL-PCBs with a persistent nature and direct evidence of exposure to humans were officially reevaluated and assigned a toxicity equivalent factor (TEF) [2, 115]. The TEF concept includes a series of compounds that meet several criteria, including structural similarity to PCDD/Fs, the

capability to bind and activate AHR, and persistence and bioaccumulation in the food chain [115].

In addition to TEF-included compounds, other compounds with dioxin-like properties still need to be evaluated for inclusion into TEF concept, such as PCB-37, hexachlorobenzene [116, 117], polychlorinated naphthalenes (PCNs) and polybrominated naphthalenes (PBNs) [2]. According to the notion that DLCs share a similar structure to dioxins and exert their toxicity predominantly through AHR, a series of emerging DLCs (e.g., PHCZs [118] and PCDPSs [119]) have been identified in distinct environmental matrices and organisms. Moreover, there are still many compounds that have been predicted to have AHR binding potential by QSAR, suggesting that they may activate/block AHR or exert dioxin-like toxicity [120]. However, the environmental concentration, bioavailability, toxicity, and potential molecular mechanism of these compounds are largely unknown.

Since many emerging DLCs have been found to elicit effects similar to dioxin at the physiological or molecular level [14, 121, 122], as a simplified method, the TEF concept is rather helpful for providing an estimate of the toxic potency, but cannot provide an assessment of the whole toxicity landscape. For example, non-dioxin-like PCBs have been observed to induce developmental neurotoxicity, although they have not been classified as the most toxic PCBs involved in the TEF concept [123]. Recent research has declared that ‘one TEF concept does not fit all’ because there may be differences in the diversity of congener-specific disturbances of biological processes [124]. Due to these limitations, a thorough investigation of emerging DLCs should be undertaken. As the concept of dioxin-like compounds is relatively large, we focus on PHCZs, PCDPSs, PCNs, polybrominated diphenyl ethers (PBDEs) and analogs in this review.

5.2 Toxicity of emerging DLCs

5.2.1 Polyhalogenated carbazoles (PHCZs)—PHCZs are a series of halogen-substituted carbazole congeners generated by natural (e.g., forest fires, volcanic eruptions, and enzymatic synthesis) or industrial processes (e.g., electronic devices, dyes, and pharmaceutical industrials). Their occurrence has already been found in various environmental matrices across the globe (e.g., up to 46.3 ng/g dw in sediments; 1.5-15.9 ng/g dw in soil from electronic-waste dismantling regions). As a novel class of environmental contaminants, they are of increasing concern (Table 1). A toxicology study in zebrafish has indicated that certain congeners (27-BCZ and 2367-CCZ) can induce swollen yolk sacs, elongated and unlooped hearts, and pericardial sac edema [125]. These adverse outcomes are similar to the cardiotoxic effects induced by TCDD and are indicated to be AHR-dependent by knocking down AHR2 [125]. *In vitro*, many PHCZ congeners show obvious CYP1A1 and 1B1 induction; furthermore, their magnitudes of response are similar to that of TCDD. The *in silico* molecular docking results indicate that certain PHCZ congeners can bind within the LBD utilizing the pose similar to TCDD, which supports the notion that PHCZs can be ligands of AHR and function through AHR [14]. After an initial toxicity screen, certain congeners (27-BCZ and 36-BCZ) with greater toxic potential have been further investigated for other physiological effects (developmental toxicity and cardiotoxicity) as well as to determine their underlying mechanisms, such as epigenetics and

transcriptomic alterations [27, 126]. Interestingly, most tested PHCZs congeners induced AHR downstream genes (e.g., CYP1A1). However, the differential effects of PHCZs as compared with TCDD is also revealed in that expression of AHRR (a sensitive AHR target gene usually up-regulated by TCDD) is down-regulated by 50% of the tested PHCZs congeners [127]. In addition to their AHR-mediated effects, estrogen receptor (ER)-, glucocorticoid receptor (GR)-, and mineralocorticoid receptor (MR)-based reporter gene assays have revealed the endocrine disruption potential of PHCZs, especially through the ER [13].

5.2.2 Polychlorinated diphenyl sulfides (PCDPSs)—PCDPSs, produced by incomplete combustion of wastes or other sorts of high-temperature processes[128], are a series of sulfur analogs of polychlorinated diphenyl ethers (PCDEs) and have dioxin-like toxic potential due to their structural similarity (Table 1). They include 209 congeners, and many of them can be detected in various environmental matrices (e.g., 0.10-6.89 ng/g dw in sediments and 0.18-0.21 ng/L in surface water of Yangtze River) [119]. Modeling data suggest that PCDPSs have bioaccumulation potential (i.e., most congeners' log *K*ow > 5) and are environmentally persistent with half-lives of 120 days in the air, 6 months in water, and 12 months in soil [129, 130]. Toxicology studies have shown that PCDPSs can induce adverse effects, including but not limited to producing oxidative stress [119], inhibiting antioxidant enzyme activity [131], and inhibiting growth [132]. Some of the toxic effects of PCDPSs are mediated by AHR [121], and transactivation assays estimate that PCDPSs can activate human AHR as well as AHR homologs in avian species (chicken, ring-necked pheasant, and Japanese quail) with distinct potencies, indicating that activation is species-specific [104]. As a result, the AHR activation potencies of some PCDPSs are even greater than the WHO-TEFs of OctaCDD, OctaCDF, and most coplanar PCBs [104].

5.2.3 Polybrominated diphenyl ethers (PBDEs) and their metabolites and analogs—PBDEs are a series of chemicals widely used since the 1970s as flame retardants in textiles, paints, furniture, and electronic products (Table 1). Despite the bans issued by regulatory actions, the massive reserves still lead to continuous release at present [133]. Particularly, in certain e-waste dismantling regions, high-level PBDEs contamination has been reported, prompting additional concern [134]. PBDEs are widely distributed in various environmental matrices, wildlife, and humans [135], and they and their metabolites can interfere with some endocrine nuclear receptors (e.g., ER [136], TR [137], etc.) and influence a variety of physiological processes [138, 139]. Moreover, some PBDEs and analogs can interact with AHR. Both *in vitro* and *in vivo* assays have revealed that PBDEs and their analogs can induce CYP1A expression or AHR-mediated reporter gene expression [140, 141]. Certain PBDE congeners have been confirmed to bind to AHR with low to moderate affinity [113]. A theoretical investigation has illuminated the potential AHR binding property of PBDEs and indicated that they contact via π-π stacking, and electron polarization may be involved in AHR binding, with Phe289, Phe345, and His285 being structurally required [142]. However, the final activity of PBDEs, as indicated by CYP1A expression, EROD, or other reporters, is still not clear. In various cell lines (MCF-7, HepG2, and H4IIE), certain PBDE congeners (BDE47, 77, 99, 100, 153, 154, 183, and 209) lead to no obvious induction of EROD or CYP1A expression. In addition, PBDE congeners exert antagonistic effects when coexposed with the potent agonist TCDD, both by interfering with the AHR interaction and the DNA

binding process [143]. Based on these human and mouse models, the current opinion is that PBDEs possibly bind AHR but do not elicit transactivation [113, 141, 143]. However, in the zebrafish ZFL cell line, evidence indicates that certain PBDE congeners, such as BDE99, can activate AHR [144]. However, the results indicate that the active congener possibly acts as a transient and weak activator. Taken together, results indicate that PBDEs may not be potent activators of AHR in human or rodent models but may be partial weak agonists or antagonists. In addition, their species- or congener-specific effects still need further examination.

For PBDE metabolites and analogs such as OH-PBDEs and MeO-PBDEs, the situation is quite different, and more obvious AHR activity can be observed. In the H4IIE cell-based transactivation assay, many PBDE analogs are capable of activating AHR and eliciting 5.0% to 101.8% of the TCDD response, with potencies ranging from 7.35×10^{-12} to 4.00×10^{-4}. It has also been found, by comparing 6-HO-BDE-47, 5-Cl-6-HO-BDE-47, 6-HO-BDE-137, and 5-Cl-6-MeO-BDE-47, that slight alterations in the PBDE analog structure can alter the activation potency [141]. Generally, HO-PBDEs can induce greater dioxin-like activity than their corresponding MeO-PBDEs [141]. Moreover, these analogs specifically induce various adverse effects at both the molecular and physiological levels (e.g., endocrine disruption [145] and developmental disruption[138]).

5.2.4 Polychlorinated naphthalenes (PCNs)—

PCNs (Table 1), including up to 75 congeners, were listed in Annexes A and C to the Stockholm Convention on Persistent Organic Pollutants in 2015. The most toxic congeners of all known PCNs are hexachloronaphthalenes (e.g., PCN66 and PCN70) as determined by the DR-CALUX assay [146]. PCNs were once largely used but are now banned in most countries due to their structural and potential toxicity similarity to dioxins [147]. AHR activation by PCNs is an important mode of action. A recent screen revealed that 31 out of 42 tested PCN congeners have dioxin-like activity, and their relative potencies range from 1.2×10^{-7} to 0.0051, which are equal to or higher than WHO-TEFs of some PCBs [146]. Similar to other DLCs, PCNs can induce multiple effects not limited to activating AHR/inducing CYP1A, including hepatotoxicity, neurotoxicity [148], and endocrine disturbances [149]. Due to their legacy and unintentional generation by technical formulations, impurities in PCBs, and release from thermal processes, a recent determination of their presence in human food and human milk indicates health risks to humans [150]. The data have indicated that PCNs have potential health impacts; although their cancer risk to infants is not significant, the noncarcinogenic adverse health effects of PCNs should not be neglected [150]. As once there was no sufficient exposure data for PCNs on humans in the early days of their use, PCNs were not included in the TEF concept [2] However, presently, an increasing number of human samples [150] as well as food [147] and environmental [151] sources of exposure data have been published, pointing out their toxic potential and the need for further research.

6. Evaluation of AHR activation/AHR-mediated toxicity

For environmental scientists, the AHR pathway is vital both for toxicity evaluation and mechanism exploration. The prototypical biomarker CYP1A, for the most part, can be used as an indicator of AHR activation but does not always indicate toxic potential [152]. The

toxicity of some DLCs has gradually been revealed, but in contrast to traditional dioxins and DL-PCBs, research on emerging DLCs is insufficient. Most scientific data are related to toxicity quantification using molecular endpoints or phenotypic effects. However, AHR, as a mediator of DLC toxicity, has many transactivation stages and mechanistic complexity (e.g., species-, ligand-, and tissue-specific variations), which prevent researchers from simply obtaining unified data for all situations. Therefore, to comprehensively understand traditional/emerging DLCs and evaluate their toxicity, many bioassays have been developed as described below.

6.1 Species-specific AHR evaluation

Generally, in research, AHR and its downstream effects mainly refer to those in human or rodent models, since their AHR pathways are relatively well characterized. However, certain metazoan species in which AHR genes have been identified may not be equally sensitive to dioxins and DLCs according to both theoretical speculation and experimental observations. The reasons for the difference in sensitivity could lie in the aspects of AHR sequence differences, the number of homologs, and AHR subform properties (e.g., expression level, predominance, and sensitivity) within or among species (Figure 2) [1, 42]. All these aspects can interfere with the results of toxicity evaluation of dioxins/DLCs and should be considered when performing ecotoxicology research on various species. Regarding emerging DLCs, most toxic studies are performed by evaluating certain biomarkers using human or mouse models. As AHR largely accounts for the sensitivity of a species to DLCs, functional characterization of AHRs from distinct species would provide evidence for evaluating the potential toxicity of DLCs on a certain species [153]. Species-specific evaluation includes traditional exposure experiments conducted *in vivo* or cloning and then artificially expressing a certain AHR *in vitro* and performing biochemical assays, such as those described for evaluating the effects of PCDPSs on AHRs of various species [104].

6.2 Ligand-AHR interaction

Since ligand binding is the initial step of AHR activation and leads to subsequent downstream effects, examining the interaction of a potential ligand with AHR is an important aspect of toxicity evaluation. Using a saturation binding assay, ligand-AHR interaction can be assessed directly, including examining the binding properties of radiolabeled ligands (e.g., TCDD [3], 2-azido-3-iodo-7,8-dibromodibenzo-p-dioxin [154], beta-naphthoflavone [32], 2-(1'*H*-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) [155], or kynurenine [156]) or examining whether an uncharacterized AHR is capable of binding one of these ligands [153, 157–159]. In addition, some indirect methods such as competitive binding assays have been developed to assess the AHR-binding activity of unlabeled ligands, such as described in Murray et al., who used a photoaffinity binding assay [154, 160] to evaluate the competitive binding of α-naphthoflavone (α-NF) and several derivatives [112]. For the characterization of the binding properties of kynurenine with AHR, using radioligand-binding assays with mouse liver cytosol from AHR-deficient and AHR-proficient mice, the equilibrium dissociation constant K_d of kynurenine binding to AHR has been determined to be approximately 4 μM [156]. With respect to receptor characterization, numerous AHR homologs (including some mutated homologs) from species across taxa have been functionally characterized [22, 24, 157, 161, 162]. Interestingly, by comparing the

LBD of AHR homologs between bird species, the key residues (Val-325 and Ala-381) were found responsible for the reduced activity of tern AHR as compared to the chicken AHR [153] and, subsequently, to determine differences in activity of AHRs in dozens of other bird species[23]. Similarly, by comparing intraspecies AHRs, some ecology-relevant issues have been resolved, such as deciphering the possible mechanism of the PCB tolerance of a certain Atlantic tomcod population in the Hudson River, which largely depends on the key residue loss in the LBD [22].

6.3 AHR-DRE binding

During the AHR transactivation process, AHR-DRE binding is a vital variable that can be altered by distinct ligands [41]. Using gel retardation assays, 1,2-naphthoquinone (1,2-NQ) and 1,4-naphthoquinone (1,4-NQ) have been examined to determine whether they can directly activate AHR [28]. To investigate wild-type, artificially mutated, or recombined AHR forms, this assay has been implemented to determine the key structural mechanism underlying AHR activation [15], such as determining the residues that determine ligand efficacy. By testing mutated forms of mouse AHR, the F281A mutant AHR was shown to be constitutively active (ligand-independent) for DNA binding but was less active than wild-type AHR. The K284A mutant AHR has an increased level of DNA binding compared with wild-type AHR, suggesting that K284A may alter the DNA binding mechanism or potency [15]. Note that the AHR-DRE binding activity is ligand-specific [28, 41]. The DNA-binding activity with non-canonical DREs (Section 3.2) needs further investigation.

6.4 Biomarkers or cell-based bioassays

6.4.1 CYP1A and EROD—CYP1A is a widely used biomarker for DLC toxicity evaluation and mechanistic exploration. The expression level of CYP1A along with its catalytic capability (indicated by EROD assay) can be indicators of AHR activation. In most cases of toxic dioxin-like HAHs, a chemical's potency for inducing CYP1A expression parallels its toxic potential, which also serves as the theoretical basis for the TEF concept [2]. However, CYP1A induction should be carefully used when evaluating a potential ligand, as some ligands that induce CYP1A do not have dioxin-like toxicity (e.g., the, RMAHRLs) [99, 152, 155, 163, 164]. Moreover, after the initial identification of CYP1A induction, a more comprehensive exploration of the tested ligands should be performed, such as performed in exploring PHCZ toxicity [125].

6.4.2 Reporter gene assays—*In vitro* screening or evaluation is usually the most efficient way to screen candidate compounds and provide initial knowledge about their toxic potential. The reporter gene assay represents a kind of method that meets the demand for toxicity evaluation or screening with the features of low cost, fast response, easy handling, etc. [165] The reporters widely used in AHR evaluation include fluorescent proteins (e.g., GFP, YFP, etc.) and enzymes (e.g., *lacZ* (β-galactosidase), *luxAB* (bacterial luciferase), firefly luciferase, etc.) [166]. At present, reporter gene assays, especially luciferase-based assays, are widely used for official screening of food and feed [167] or for the identification and toxicity evaluation of some suspected compounds [26, 104]. In addition, other alternative methods, such as FRET, fluorescent-conjugated antibodies, and fusion proteins (e.g., AHR-YFP/GFP), can be used for cellular imaging, measuring the degree of AHR activation, examining the AHR-

ARNT interaction, and figuring out the AHR subcellular location/translocation [168, 169]. To date, these methods are undergoing continuous updates to meet multiple detection demands and improve future research on DLCs.

6.5 In vivo/ex vivo evaluation assays

In vivo/ex vivo methods are another class of tools for evaluating AHR-mediated toxicity and are usually based on wild-type or transgenic models. As implemented in identifying novel DLCs, exposing zebrafish embryos to PHCZs results in phenotypic alterations/toxicity similar to that of TCDD, suggesting that PHCZs function through a similar mechanism to TCDD [125]. By comparing wild-type and AHR-knockout mice or rats exposed to TCDD, many physiological parameters (e.g., bile acid metabolism [170] and B cell responses [171]) have been observed to be distinctively altered, indicating the role of AHR. While examining the sensitivity of the AHR of an unidentified species, the *ex vivo* exposure method with precision-cut liver slices (PCLS) is direct and rapid and can help to evaluate the AHR sensitivity and gene expression in a certain species, such as in characterizing the Atlantic Cod AHR1a and AHR2a [29]. To investigate DLCs' influences on various organs/tissues, immunohistochemical imaging of CYP1A expression as well as a type of artificial transgenic reporter would help to identify potential toxicity targets [140, 172]. By determining molecular and physiological markers, distinct toxic response patterns and tissue-specific patterns can be revealed.

6.6 Omics-based examination

CYP1A expression is the gold standard for AHR ligand evaluation, for instance, in indicating agonist/antagonist activities and their enhancement or inhibition of AHR-dependent physiological function [96]. CYP1A expression is easy to use but sometimes is not that informative or have a direct relationship with the adverse outcomes. Thus, attempts have been made to use systems biology to gain comprehensive insight into the potential impacts of ligands of interest [173], which also directly supports the idea that they have the potential to induce ligand-specific effects in addition to just activating AHR [174]. By using a novel human reduced transcriptomics (RHT) approach to assess pathway-based profiles of AHR ligands, several ligands' (i.e., TCDD, TCS, and 5-Cl-6-HO-BDE47) toxic mechanisms have been revealed [175]. This method provides direct support that the AHR pathway is the major pathway induced by TCDD. For 5-Cl-6-HO-BDE47, the AHR pathway is less sensitively induced than the 'stress response'-related pathway. The authors suspect that 5-Cl-6-HO-BDE47 may initiate multiple biological events as early responses and not just induce AHR activation, which is thought to be a secondary effect [175].

In addition to the above-mentioned methods, other methods, such as *in silico* simulation or biochemical assays (e.g., ELISA), are also helpful for evaluating the AHR activation potential or AHR-relevant parameters. As the protein structure of AHR has not been fully resolved, current simulations are based on homology modeling and need to be further validated by biochemical assays. By virtue of the numerous AHR sequences of distinct species, modeling enables the characterization of the key residues within the LBD of the AHR of interest that interact with potential ligands [42]. With regard to ligands, QSAR models

based on multiple physicochemical parameters can predict the potential binding affinity of suspected compounds and provide factors that influence their binding [120].

7. Summary and perspectives

Currently, the elucidation of AHR-related effects, mechanisms, and methods have for the most part been investigated using the classical ligand TCDD. The information obtained provides an important starting point when conducting similar research on other compounds. However, the effects and specific mechanisms of toxicity of emerging DLCs are possibly different from those of TCDD and thus need thorough consideration for chemical-specific variation in the role of AHR in mediating their effects.

For those DLCs, AHR mediation is one of the most fundamental mechanisms. DLCs have diverse toxic effects, which may rely on their corresponding physicochemical properties. Moreover, when considering the AHR, the AHR-ligand interaction (e.g., the binding affinity, binding pose, and structural change of the LBD), DNA recognition and cofactor recruitment are fundamental for the diverse outcomes of DLCs. Although some major motifs or domains of AHR have been defined and preliminarily functionally characterized, the knowledge of AHR is still limited when generating or predicting the potential correlation between AHR structure/sequence and its function or sensitivity. Besides, we also need to investigate AHR holistically, although certain parts of AHR already have ‘widely accepted’ functions, since even subtle changes in AHR or ligands may greatly alter subsequent functions or outcomes.

For these reasons, and the inter-species sequence dissimilarity, the diversity of AHR homologs of distinct species would be of another great interest especially when evaluating the DLC ecotoxicity. However, we currently have limited knowledge and lack a uniform method to clearly specify the sensitivity differences among species to various DLCs. Regarding this aspect, future research may need to focus on developing some new assays that could be easily set up and flexibly extend the usage on cross-species DLC evaluation or even the properties of the candidate AHR itself.

In summary, the current toxicology research on DLCs mostly concerns some basic toxic endpoints and the bioassay-determined potential to elicit certain molecular- or (sometimes) physiological-level effects. Thus, more detailed information on the mechanisms/effects of DLCs on wildlife and humans is expected. As we learn more about these emerging, structurally diverse DLCs, understanding the diversity of AHR-mediated mechanisms involved in their toxicity is both an important and a fascinating area of research. Advances in understanding AHR biology will help advance understanding of the toxicology of these emerging DLCs.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (No. 22006049), and the U.S. National Institute of Environmental Health Sciences (NIEHS) (P42ES007381 and R01ES032323).

All the authors wrote and revised this paper. The authors declare no competing financial interests.

References

1. Hahn ME; Karchner SI; Merson RR, Diversity as opportunity: insights from 600 million years of AHR evolution. Curr. Opin. Toxicol 2017, 2, 58–71. [PubMed: 28286876]
2. van den Berg M; Birnbaum LS; Denison MS; De Vito M; Farland W; Feeley M; Fiedler H; Hakansson H; Hanberg A; Haws L, The 2005 World Health Organization reevaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol. Sci 2006, 93, (2), 223–241. [PubMed: 16829543]
3. Poland A; Glover E; Kende AS, Stereospecific, high affinity binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin by hepatic cytosol. Evidence that the binding species is receptor for induction of aryl hydrocarbon hydroxylase. J. Biol. Chem 1976, 251, (16), 4936–4946. [PubMed: 956169]
4. Weijs L; Losada S; Das K; Roosens L; Reijnders PJH; Santos JF; Neels H; Blust R; Covaci A, Biomagnification of naturally-produced methoxylated polybrominated diphenyl ethers (MeO-PBDEs) in harbour seals and harbour porpoises from the Southern North Sea. Environ. Int 2009, 35, (6), 893–899. [PubMed: 19375800]
5. Wu Y; Tan H; Sutton R; Chen D, From sediment to top predators: broad exposure of polyhalogenated carbazoles in San Francisco Bay (U.S.A.). Environ. Sci. Technol 2017, 51, (4), 2038–2046. [PubMed: 28112952]
6. Zhang X; Fang B; Wang T; Liu H; Feng M; Qin L; Zhang R, Tissue-specific bioaccumulation, depuration and metabolism of 4,4′-dichlorodiphenyl sulfide in the freshwater mussel Anodonta woodiana. Sci. Total Environ 2018, 642, 854–863. [PubMed: 29925056]
7. Guo Z; Xie HQ; Zhang P; Luo Y; Xu T; Liu Y; Fu H; Xu L; Valsami-Jones E; Boksa P; Zhao B, Dioxins as potential risk factors for autism spectrum disorder. Environ. Int 2018, 121, 906–915. [PubMed: 30347373]
8. Chen Y; Sha R; Xu L; Xia Y; Liu Y; Li X; Xie HQ; Tang N; Zhao B, 2,3,7,8-Tetrachlorodibenzo-p-dioxin promotes migration ability of primary cultured rat astrocytes via aryl hydrocarbon receptor. J. Environ. Sci 2019, 76, 368–376.
9. Li Y; Xie HQ; Zhang W; Wei Y; Sha R; Xu L; Zhang J; Jiang Y; Guo TL; Zhao B, Type 3 innate lymphoid cells are altered in colons of C57BL/6 mice with dioxin exposure. Sci. Total Environ 2019, 662, 639–645. [PubMed: 30703721]
10. Ben Hassine S; Ben Ameur W; Eljarrat E; Barceló D; Touil S; Driss MR, Methoxylated polybrominated diphenyl ethers (MeO-PBDE) in human milk from Bizerte, Tunisia. Environ. Res 2015, 138, 32–37. [PubMed: 25682256]
11. Schultz IR; Kuo LJ; Cullinan V; Cade S, Occupational and dietary differences in hydroxylated and methoxylated PBDEs and metals in plasma from Puget Sound, Washington, USA region volunteers. Sci. Total Environ 2020, 714, 136566. [PubMed: 31981866]
12. Wang G; Jiang T; Li S; Hou H; Xiao K; Hu J; Liang S; Liu B; Yang J, Occurrence and exposure risk evaluation of polyhalogenated carbazoles (PHCZs) in drinking water. Sci. Total Environ 2021, 750, 141615. [PubMed: 32858294]
13. Yue S; Zhang T; Shen Q; Song Q; Ji C; Chen Y; Mao M; Kong Y; Chen D; Liu J; Sun Z; Zhao M, Assessment of endocrine-disrupting effects of emerging polyhalogenated carbazoles (PHCZs): In vitro, in silico, and in vivo evidence. Environ. Int 2020, 140, 105729. [PubMed: 32344252]
14. Ma D; Xie HQ; Zhang W; Xue Q; Liu X; Xu L; Ma Y; Bonefeld-Jørgensen EC; Long M; Zhang A; Zhao B, Aryl hydrocarbon receptor activity of polyhalogenated carbazoles and the molecular mechanism. Sci. Total Environ 2019, 687, 516–526. [PubMed: 31216508]
15. Soshilov AA; Motta S; Bonati L; Denison MS, Transitional states in ligand-dependent transformation of the aryl hydrocarbon receptor into its DNA-binding form. Int. J. Mol. Sci 2020, 21, (7), 2474.
16. Seok S; Lee W; Jiang L; Molugu K; Zheng A; Li Y; Park S; Bradfield CA; Xing Y, Structural hierarchy controlling dimerization and target DNA recognition in the AHR transcriptional complex. PNAS 2017, 114, (21), 5431. [PubMed: 28396409]
17. Andersson P; McGuire J; Rubio C; Gradin K; Whitelaw ML; Pettersson S; Hanberg A; Poellinger L, A constitutively active dioxin/aryl hydrocarbon receptor induces stomach tumors. PNAS 2002, 99, (15), 9990–9995. [PubMed: 12107286]

18. Moura-Alves P; Fae K; Houthuys E; Dorhoi A; Kreuchwig A; Furkert J; Barison N; Diehl A; Munder A; Constant P; Skrahina T; Guhlich-Bornhof U; Klemm M; Koehler A; Bandermann S; Goosmann C; Mollenkopf H; Hurwitz R; Brinkmann V; Fillatreau S; Daffe M; Tuemmler B; Kolbe M; Oschkinat H; Krause G; Kaufmann SHE, AhR sensing of bacterial pigments regulates antibacterial defence. Nature 2014, 512, (7515), 387–392. [PubMed: 25119038]
19. Bessede A; Gargaro M; Pallotta MT; Matino D; Servillo G; Brunacci C; Bicciato S; Mazza EMC; Macchiarulo A; Vacca C; Iannitti R; Tissi L; Volpi C; Belladonna ML; Orabona C; Bianchi R; Lanz TV; Platten M; Della Fazia MA; Piobbico D; Zelante T; Funakoshi H; Nakamura T; Gilot D; Denison MS; Guillemin GJ; DuHadaway JB; Prendergast GC; Metz R; Geffard M; Boon L; Pirro M; Iorio A; Veyret B; Romani L; Grohmann U; Fallarino F; Puccetti P, Aryl hydrocarbon receptor control of a disease tolerance defence pathway. Nature 2014, 511, (7508), 184–190. [PubMed: 24930766]
20. Mulero-Navarro S; Fernandez-Salguero PM, New trends in aryl hydrocarbon receptor biology. Front. Cell Dev. Biol 2016, 4, 45. [PubMed: 27243009]
21. Hahn ME; Sadler KC, Casting a wide net: use of diverse model organisms to advance toxicology. Dis. Model Mech 2020, 13, (4).
22. Wirgin I; Roy NK; Loftus M; Chambers RC; Franks DG; Hahn ME, Mechanistic basis of resistance to PCBs in Atlantic tomcod from the Hudson River. Science 2011, 331, (6022), 1322–1325. [PubMed: 21330491]
23. Farmahin R; Manning GE; Crump D; Wu D; Mundy LJ; Jones SP; Hahn ME; Karchner SI; Giesy JP; Bursian SJ; Zwiernik MJ; Fredricks TB; Kennedy SW, Amino acid sequence of the ligand-binding domain of the aryl hydrocarbon receptor 1 predicts sensitivity of wild birds to effects of dioxin-like compounds. Toxicol. Sci 2013, 131, (1), 139–52. [PubMed: 22923492]
24. Lavine JA; Rowatt AJ; Klimova T; Whitington AJ; Dengler E; Beck C; Powell WH, Aryl hydrocarbon receptors in the frog Xenopus laevis: two AhR1 paralogs exhibit low affinity for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol Sci 2005, 88, (1), 60–72. [PubMed: 15958654]
25. Larsson M; van den Berg M; Brenerová P; van Duursen MB; van Ede KI; Lohr C; Luecke-Johansson S; Machala M; Neser S; Pěnčíková K; Poellinger L; Schrenk D; Strapáčová S; Vondráček J; Andersson PL, Consensus toxicity factors for polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls combining in silico models and extensive in vitro screening of AhR-mediated effects in human and rodent cells. Chem. Res. Toxicol 2015, 28, (4), 641–650. [PubMed: 25654323]
26. Zhang S; Li S; Zhou Z; Fu H; Xu L; Xie HQ; Zhao B, Development and application of a novel bioassay system for dioxin determination and aryl hydrocarbon receptor activation evaluation in ambient-air samples. Environ. Sci. Technol 2018, 52, (5), 2926–2933. [PubMed: 29437390]
27. Ji C; Yan L; Chen Y; Yue S; Dong Q; Chen J; Zhao M, Evaluation of the developmental toxicity of 2,7-dibromocarbazole to zebrafish based on transcriptomics assay. J. Hazard. Mater 2019, 368, 514–522. [PubMed: 30710780]
28. Faber SC; Giani Tagliabue S; Bonati L; Denison MS, The cellular and molecular determinants of naphthoquinone-dependent activation of the aryl hydrocarbon receptor. Int. J. Mol. Sci 2020, 21, (11), 4111.
29. Aranguren-Abadía L; Lille-Langøy R; Madsen AK; Karchner SI; Franks DG; Yadetie F; Hahn ME; Goksøyr A; Karlsen OA, Molecular and functional properties of the Atlantic cod (Gadus morhua) aryl hydrocarbon receptors Ahr1a and Ahr2a. Environ. Sci. Technol 2020, 54, (2), 1033–1044. [PubMed: 31852180]
30. Sakurai S; Shimizu T; Ohto U, The crystal structure of the AhRR-ARNT heterodimer reveals the structural basis of the repression of AhR-mediated transcription. J. Biol. Chem 2017, 292, (43), 17609–17616. [PubMed: 28904176]
31. Powell-Coffman JA; Bradfield CA; Wood WB, Caenorhabditis elegans orthologs of the aryl hydrocarbon receptor and its heterodimerization partner the aryl hydrocarbon receptor nuclear translocator. PNAS 1998, 95, (6), 2844–9. [PubMed: 9501178]
32. Butler RA; Kelley ML; Powell WH; Hahn ME; Van Beneden RJ, An aryl hydrocarbon receptor (AHR) homologue from the soft-shell clam, Mya arenaria: evidence that invertebrate AHR

homologues lack 2,3,7,8-tetrachlorodibenzo-p-dioxin and beta-naphthoflavone binding. Gene 2001, 278, (1-2), 223–34. [PubMed: 11707340]

33. Powell-Coffman JA; Qin H, Invertebrate AHR Homologs: Ancestral Functions in Sensory Systems. In The AH Receptor in Biology and Toxicology, 2011; pp 405–411.
34. Denison MS; Faber SC, And now for something completely different: diversity in ligand-dependent activation of ah receptor responses. Curr. Opin. Toxicol 2017, 2, 124–131. [PubMed: 28845473]
35. Wright EJ; De Castro KP; Joshi AD; Elferink CJ, Canonical and non-canonical aryl hydrocarbon receptor signaling pathways. Curr. Opin. Toxicol 2017, 2, 87–92. [PubMed: 32296737]
36. Jackson DP; Joshi AD; Elferink CJ, Ah receptor pathway intricacies; signaling through diverse protein partners and DNA-motifs. Toxicol. Res 2015, 4, (5), 1143–1158.
37. Ge NL; Elferink CJ, A direct interaction between the aryl hydrocarbon receptor and retinoblastoma protein. Linking dioxin signaling to the cell cycle. J. Biol. Chem 1998, 273, (35), 22708–22713. [PubMed: 9712901]
38. Soshilov A; Denison MS, Role of the Per/Arnt/Sim domains in ligand-dependent transformation of the aryl hydrocarbon receptor. J. Biol. Chem 2008, 283, (47), 32995–33005. [PubMed: 18806268]
39. Alessandro P; Denison MS; Yujuan S; Soshilov AA; Laura B, Structural and functional characterization of the aryl hydrocarbon receptor ligand binding domain by homology modeling and mutational analysis. Biochemistry 2007, 46, (3), 696. [PubMed: 17223691]
40. Bisson WH; Koch DC; O'Donnell EF; Khalil SM; Kerkvliet NI; Tanguay RL; Abagyan R; Kolluri SK, Modeling of the aryl hydrocarbon receptor (AhR) ligand binding domain and its utility in virtual ligand screening to predict new AhR ligands. J. Med. Chem 2009, 52, (18), 5635–41. [PubMed: 19719119]
41. Giani Tagliabue S; Faber SC; Motta S; Denison MS; Bonati L, Modeling the binding of diverse ligands within the Ah receptor ligand binding domain. Sci. Rep 2019, 9, (1), 10693. [PubMed: 31337850]
42. Zhang W; Xie HQ; Li Y; Zou X; Xu L; Ma D; Li J; Ma Y; Jin T; Hahn ME; Zhao B, Characterization of the aryl hydrocarbon receptor (AhR) pathway in Anabas testudineus and mechanistic exploration of the reduced sensitivity of AhR2a. Environ. Sci. Technol 2019, 53, (21), 12803–12811. [PubMed: 31566365]
43. Pohjanvirta R; Wong JM; Li W; Harper PA; Tuomisto J; Okey AB, Point mutation in intron sequence causes altered carboxyl-terminal structure in the aryl hydrocarbon receptor of the most 2,3,7,8-tetrachlorodibenzo-p-dioxin-resistant rat strain. Mol. Pharmacol 1998, 54, (1), 86–93. [PubMed: 9658193]
44. Korkalainen M; Tuomisto J; Pohjanvirta R, Restructured transactivation domain in hamster AH receptor. Biochem. Biophys. Res. Commun 2000, 273, (1), 272–81. [PubMed: 10873598]
45. Riddell N; Jin UH; Safe S; Cheng Y; Chittim B; Konstantinov A; Parette R; Pena-Abaurrea M; Reiner EJ; Poirier D; Stefanac T; McAlees AJ; McCrindle R, Characterization and biological potency of mono- to tetra-halogenated carbazoles. Environ. Sci. Technol 2015, 49, (17), 10658–10666. [PubMed: 26226543]
46. Kopec AK; Burgoon LD; Ibrahim-Aibo D; Burg AR; Lee AW; Tashiro C; Potter D; Sharratt B; Harkema JR; Rowlands JC; Budinsky RA; Zacharewski TR, Automated dose-response analysis and comparative toxicogenomic evaluation of the hepatic effects elicited by TCDD, TCDF, and PCB126 in C57BL/6 mice. Toxicol. Sci 2010, 118, (1), 286–297. [PubMed: 20702594]
47. Zhang S; Rowlands C; Safe S, Ligand-dependent interactions of the Ah receptor with coactivators in a mammalian two-hybrid assay. Toxicol. Appl. Pharmacol 2008, 227, (2), 196–206. [PubMed: 18048071]
48. Josyula N; Andersen ME; Kaminski NE; Dere E; Zacharewski TR; Bhattacharya S, Gene co-regulation and co-expression in the aryl hydrocarbon receptor-mediated transcriptional regulatory network in the mouse liver. Arch. Toxicol 2020, 94, (1), 113–126. [PubMed: 31728591]
49. Vogel CF; Sciullo E; Li W; Wong P; Lazennec G; Matsumura F, RelB, a new partner of aryl hydrocarbon receptor-mediated transcription. Mol. Endocrinol 2007, 21, (12), 2941–2955. [PubMed: 17823304]

50. Jackson DP; Li H; Mitchell KA; Joshi AD; Elferink CJ, Ah receptor–mediated suppression of liver regeneration through NC-XRE–driven p21Cip1 expression. Mol. Pharmacol 2014, 85, (4), 533–541. [PubMed: 24431146]
51. Ohtake F; Takeyama K; Matsumoto T; Kitagawa H; Yamamoto Y; Nohara K; Tohyama C; Krust A; Mimura J; Chambon P; Yanagisawa J; Fujii-Kuriyama Y; Kato S, Modulation of oestrogen receptor signalling by association with the activated dioxin receptor. Nature 2003, 423, (6939), 545–550. [PubMed: 12774124]
52. Watabe Y; Nazuka N; Tezuka M; Shimba S, Aryl hydrocarbon receptor functions as a potent coactivator of E2F1-dependent trascription activity. Biol. Pharm. Bull 2010, 33, (3), 389–397. [PubMed: 20190398]
53. Ohtake F; Baba A; Takada I; Okada M; Iwasaki K; Miki H; Takahashi S; Kouzmenko A; Nohara K; Chiba T; Fujii-Kuriyama Y; Kato S, Dioxin receptor is a ligand-dependent E3 ubiquitin ligase. Nature 2007, 446, (7135), 562–566. [PubMed: 17392787]
54. Jin UH; Karki K; Kim SB; Safe S, Inhibition of pancreatic cancer Panc1 cell migration by omeprazole is dependent on aryl hydrocarbon receptor activation of JNK. Biochem. Biophys. Res. Commun 2018, 501, (3), 751–757. [PubMed: 29758193]
55. Zhu J; Luo L; Tian L; Yin S; Ma X; Cheng S; Tang W; Yu J; Ma W; Zhou X; Fan X; Yang X; Yan J; Xu X; Lv CZ; Liang H, Aryl hydrocarbon receptor promotes IL-10 expression in inflammatory macrophages through Src-STAT3 signaling pathway. Front. Immunol 2018, 9. [PubMed: 29403493]
56. Brinchmann BC; Le Ferrec E; Podechard N; Lagadic-Gossmann D; Shoji KF; Penna A; Kukowski K; Kubátová A; Holme JA; Øvrevik J, Lipophilic chemicals from diesel exhaust particles trigger calcium response in human endothelial cells via aryl hydrocarbon receptor non-genomic signalling. Int. J. Mol. Sci 2018, 19, (5), 1429.
57. Chen Y; Xie HQ; Sha R; Xu T; Zhang S; Fu H; Xia Y; Liu Y; Xu L; Zhao B, 2,3,7,8-Tetrachlorodibenzo-p-dioxin and up-regulation of neurofilament expression in neuronal cells: Evaluation of AhR and MAPK pathways. Environ. Int 2020, 134, 105193. [PubMed: 31775093]
58. Assefa EG; Yan Q; Gezahegn SB; Salissou MTM; He S; Wu N; Zuo X; Ying C, Role of resveratrol on indoxyl sulfate-induced endothelial hyperpermeability via aryl hydrocarbon receptor (AHR)/Src-dependent pathway. Oxid. Med. Cell Longev 2019, 2019, 5847040. [PubMed: 31885805]
59. Henry EC; Gasiewicz TA, Agonist but not antagonist ligands induce conformational change in the mouse aryl hydrocarbon receptor as detected by partial proteolysis. Mol. Pharmacol 2003, 63, (2), 392–400. [PubMed: 12527811]
60. Faber SC; Soshilov AA; Giani Tagliabue S; Bonati L; Denison MS, Comparative in vitro and in silico analysis of the selectivity of indirubin as a human ah receptor agonist. Int. J. Mol. Sci 2018, 19, (9), 2692.
61. Sogawa K; Fujisawa-Sehara A; Yamane M; Fujii-Kuriyama Y, Location of regulatory elements responsible for drug induction in the rat cytochrome P-450c gene. PNAS 1986, 83, (21), 8044–8. [PubMed: 3464941]
62. Denison MS; Fisher JM; Whitlock JP Jr., The DNA recognition site for the dioxin-Ah receptor complex. Nucleotide sequence and functional analysis. J. Biol. Chem 1988, 263, (33), 17221–4. [PubMed: 2846558]
63. Dere E; Lo R; Celius T; Matthews J; Zacharewski TR, Integration of genome-wide computation DRE search, AhR ChIP-chip and gene expression analyses of TCDD-elicited responses in the mouse liver. BMC Genomics 2011, 12, 365. [PubMed: 21762485]
64. Dere E; Forgacs AL; Zacharewski TR; Burgoon LD, Genome-wide computational analysis of dioxin response element location and distribution in the human, mouse, and rat genomes. Chem. Res. Toxicol 2011, 24, (4), 494–504. [PubMed: 21370876]
65. Sogawa K; Numayama-Tsuruta K; Takahashi T; Matsushita N; Miura C; Nikawa J; Gotoh O; Kikuchi Y; Fujii-Kuriyama Y, A novel induction mechanism of the rat CYP1A2 gene mediated by Ah receptor–Arnt heterodimer. Biochem. Biophys. Res. Commun 2004, 318, (3), 746–755. [PubMed: 15144902]

66. Gouédard C; Barouki R; Morel Y, Dietary polyphenols increase paraoxonase 1 gene expression by an aryl hydrocarbon receptor-dependent mechanism. Mol. Cell Biol 2004, 24, (12), 5209–5222. [PubMed: 15169886]

67. Matikainen T; Perez GI; Jurisicova A; Pru JK; Schlezinger JJ; Ryu HY; Laine J; Sakai T; Korsmeyer SJ; Casper RF; Sherr DH; Tilly JL, Aromatic hydrocarbon receptor-driven Bax gene expression is required for premature ovarian failure caused by biohazardous environmental chemicals. Nat. Genet 2001, 28, (4), 355–360. [PubMed: 11455387]

68. DeGroot DE; Hayashi A; Denison MS, Lack of ligand-selective binding of the aryl hydrocarbon receptor to putative DNA binding sites regulating expression of Bax and paraoxonase 1 genes. Arch Biochem Biophys 2014, 541, 13–20. [PubMed: 24200861]

69. Hestermann EV; Stegeman JJ; Hahn ME, Relative contributions of affinity and intrinsic efficacy to aryl hydrocarbon receptor ligand potency. Toxicol. Appl. Pharmacol 2000, 168, (2), 160–72. [PubMed: 11032772]

70. Englert NA; Turesky RJ; Han W; Bessette EE; Spivack SD; Caggana M; Spink DC; Spink BC, Genetic and epigenetic regulation of AHR gene expression in MCF-7 breast cancer cells: role of the proximal promoter GC-rich region. Biochem. Pharmacol 2012, 84, (5), 722–735. [PubMed: 22728919]

71. Helmig S; Seelinger JU; Döhrel J; Schneider J, RNA expressions of AHR, ARNT and CYP1B1 are influenced by AHR Arg554Lys polymorphism. Mol. Genet. Metab 2011, 104, (1-2), 180–184. [PubMed: 21742528]

72. Aluru N; Karchner SI; Hahn ME, Role of DNA methylation of AHR1 and AHR2 promoters in differential sensitivity to PCBs in Atlantic Killifish, Fundulus heteroclitus. Aquat. Toxicol 2011, 101, (1), 288–294. [PubMed: 21111492]

73. Beedanagari SR; Taylor RT; Bui P; Wang F; Nickerson DW; Hankinson O, Role of epigenetic mechanisms in differential regulation of the dioxin-inducible human CYP1A1 and CYP1B1 genes. Mol. Pharmacol 2010, 78, (4), 608–616. [PubMed: 20631054]

74. Ikuta T; Kobayashi Y; Kawajiri K, Phosphorylation of nuclear localization signal inhibits the ligand-dependent nuclear import of aryl hydrocarbon receptor. Biochem. Biophys. Res. Commun 2004, 317, (2), 545–550. [PubMed: 15063792]

75. Ma Q; Baldwin KT, 2,3,7,8-Tetrachlorodibenzo-p-dioxin-induced degradation of aryl hydrocarbon receptor (AhR) by the ubiquitin-proteasome pathway. Role of the transcription activaton and DNA binding of AhR. J. Biol. Chem 2000, 275, (12), 8432–8438. [PubMed: 10722677]

76. Reitzel AM; Karchner SI; Franks DG; Evans BR; Nacci D; Champlin D; Vieira VM; Hahn ME, Genetic variation at aryl hydrocarbon receptor (AHR) loci in populations of Atlantic killifish (Fundulus heteroclitus) inhabiting polluted and reference habitats. BMC Evol. Biol 2014, 14, 6. [PubMed: 24422594]

77. Reid NM; Proestou DA; Clark BW; Warren WC; Colbourne JK; Shaw JR; Karchner SI; Hahn ME; Nacci D; Oleksiak MF, The genomic landscape of rapid repeated evolutionary adaptation to toxic pollution in wild fish. Science 2016, 354, (6317), 1305–1308. [PubMed: 27940876]

78. Osterberg JS; Cammen KM; Schultz TF; Clark BW; Di Giulio RT, Genome-wide scan reveals signatures of selection related to pollution adaptation in non-model estuarine Atlantic killifish (Fundulus heteroclitus). Aquat. Toxicol 2018, 200, 73–82. [PubMed: 29727773]

79. Nacci D; Proestou D; Champlin D; Martinson J; Waits ER, Genetic basis for rapidly evolved tolerance in the wild: adaptation to toxic pollutants by an estuarine fish species. Mol. Ecol 2016, 25, (21), 5467–5482. [PubMed: 27662639]

80. Li D; Liu C; Yu H; Zeng X; Xing X; Chen L; Gao C; Zhang Z; Xiao Y; Duan H; Zheng Y; Wang Q; Chen W, AhR is negatively regulated by miR-203 in response to TCDD or BaP treatment. Toxicol. Res 2014, 3, (2), 142–151.

81. Zhang W; Xie HQ; Li Y; Jin T; Li J; Xu L; Zhou Z; Zhang S; Ma D; Hahn ME; Zhao B, Transcriptomic analysis of Anabas testudineus and its defensive mechanisms in response to persistent organic pollutants exposure. Sci. Total Environ 2019, 669, 621–630. [PubMed: 30893621]

82. Mimura J; Ema M; Sogawa K; Fujii-Kuriyama Y, Identification of a novel mechanism of regulation of Ah (dioxin) receptor function. Genes. Dev 1999, 13, (1), 20–5. [PubMed: 9887096]

83. Karchner SI; Franks DG; Powell WH; Hahn ME, Regulatory interactions among three members of the vertebrate aryl hydrocarbon receptor family: AHR repressor, AHR1, and AHR2. J. Biol. Chem 2002, 277, (9), 6949–59. [PubMed: 11742002]
84. Evans BR; Karchner SI; Allan LL; Pollenz RS; Tanguay RL; Jenny MJ; Sherr DH; Hahn ME, Repression of aryl hydrocarbon receptor (AHR) signaling by AHR repressor: role of DNA binding and competition for AHR nuclear translocator. Mol. Pharmacol 2008, 73, (2), 387–398. [PubMed: 18000031]
85. Oshima M; Mimura J; Yamamoto M; Fujii-Kuriyama Y, Molecular mechanism of transcriptional repression of AhR repressor involving ANKRA2, HDAC4, and HDAC5. Biochem. Biophys. Res. Commun 2007, 364, (2), 276–282. [PubMed: 17949687]
86. MacPherson L; Ahmed S; Tamblyn L; Krutmann J; Förster I; Weighardt H; Matthews J, Aryl hydrocarbon receptor repressor and TiPARP (ARTD14) use similar, but also distinct mechanisms to repress aryl hydrocarbon receptor signaling. Int. J. Mol. Sci 2014, 15, (5), 7939–57. [PubMed: 24806346]
87. MacPherson L; Tamblyn L; Rajendra S; Bralha F; McPherson JP; Matthews J, 2,3,7,8-Tetrachlorodibenzo-p-dioxin poly(ADP-ribose) polymerase (TiPARP, ARTD14) is a mono-ADP-ribosyltransferase and repressor of aryl hydrocarbon receptor transactivation. Nucleic. Acids Res 2013, 41, (3), 1604–21. [PubMed: 23275542]
88. Wincent E; Bengtsson J; Mohammadi Bardbori A; Alsberg T; Luecke S; Rannug U; Rannug A, Inhibition of cytochrome P4501-dependent clearance of the endogenous agonist FICZ as a mechanism for activation of the aryl hydrocarbon receptor. PNAS 2012, 109, (12), 4479–84. [PubMed: 22392998]
89. Mohammadi-Bardbori A; Bengtsson J; Rannug U; Rannug A; Wincent E, Quercetin, resveratrol, and curcumin are indirect activators of the aryl hydrocarbon receptor (AHR). Chem. Res. Toxicol 2012, 25, (9), 1878–1884. [PubMed: 22867086]
90. Jeong J; Kim KH; Kim DY; Chandrasekaran G; Kim M; Pagire SH; Dighe M; Choi EY; Bak SM; Kim EY; Shin MG; Choi SY; Ahn JH, Identification of new aryl hydrocarbon receptor (AhR) antagonists using a zebrafish model. Bioorg. Med. Chem 2019, 27, (19), 115014. [PubMed: 31358358]
91. Puyskens A; Stinn A; van der Vaart M; Kreuchwig A; Protze J; Pei G; Klemm M; Guhlich-Bornhof U; Hurwitz R; Krishnamoorthy G; Schaaf M; Krause G; Meijer AH; Kaufmann SHE; Moura-Alves P, Aryl hydrocarbon receptor modulation by tuberculosis drugs impairs host defense and treatment outcomes. Cell Host Microbe. 2020, 27, (2), 238–248. [PubMed: 31901518]
92. Wu PY; Chuang PY; Chang GD; Chan YY; Tsai TC; Wang BJ; Lin KH; Hsu WM; Liao YF; Lee H, Novel Endogenous Ligands of Aryl Hydrocarbon Receptor Mediate Neural Development and Differentiation of Neuroblastoma. ACS Chem. Neurosci 2019, 10, (9), 4031–4042. [PubMed: 31404492]
93. Tian Y; Gui W; Smith PB; Koo I; Murray IA; Cantorna MT; Perdew GH; Patterson AD, Isolation and identification of aryl hydrocarbon receptor modulators in white button mushrooms (Agaricus bisporus). J. Agric. Food Chem 2019, 67, (33), 9286–9294. [PubMed: 31339733]
94. Tarnow P; Zordick C; Bottke A; Fischer B; Kühne F; Tralau T; Luch A, Characterization of quinoline yellow dyes as transient aryl hydrocarbon receptor agonists. Chem. Res. Toxicol 2020, 33, (3), 742–750. [PubMed: 31957441]
95. Murray IA; Patterson AD; Perdew GH, Aryl hydrocarbon receptor ligands in cancer: friend and foe. Nat. Rev. Cancer 2014, 14, (12), 801–814. [PubMed: 25568920]
96. Safe S; Jayaraman A; Chapkin RS, Ah receptor ligands and their impacts on gut resilience: structure-activity effects. Crit. Rev. Toxicol 2020, 1–11. [PubMed: 32162576]
97. Safe S; Jin UH; Park H; Chapkin RS; Jayaraman A, Aryl Hydrocarbon Receptor (AHR) Ligands as Selective AHR Modulators (SAhRMs). Int. J. Mol. Sci 2020, 21, (18).
98. Dolciami D; Ballarotto M; Gargaro M; López-Cara LC; Fallarino F; Macchiarulo A, Targeting Aryl hydrocarbon receptor for next-generation immunotherapies: Selective modulators (SAhRMs) versus rapidly metabolized ligands (RMAhRLs). Eur. J. Med. Chem 2020, 185, 111842. [PubMed: 31727470]

99. Ehrlich AK; Kerkvliet NI, Is chronic AhR activation by rapidly metabolized ligands safe for the treatment of immune-mediated diseases? Curr. Opin. Toxicol 2017, 2, 72–78. [PubMed: 28944315]
100. Mahiout S; Tagliabue SG; Nasri A; Omoruyi IM; Pettersson L; Bonati L; Pohjanvirta R, In vitro toxicity and in silico docking analysis of two novel selective AH-receptor modulators. Toxicol. In Vitro 2018, 52, 178–188. [PubMed: 29908305]
101. Zhang X; Fang B; Wang T; Liu H; Feng M; Qin L; Zhang R, Tissue-specific bioaccumulation, depuration and metabolism of 4,4′-dichlorodiphenyl sulfide in the freshwater mussel Anodonta woodiana. Sci. Total Environ 2018, 642, 854–863. [PubMed: 29925056]
102. Cheng J; Mao L; Zhao Z; Shen M; Zhang S; Huang Q; Gao S, Bioaccumulation, depuration and biotransformation of 4,4′-dibromodiphenyl ether in crucian carp (Carassius auratus). Chemosphere 2012, 86, (5), 446–53. [PubMed: 22036552]
103. Roy MA; Sant KE; Venezia OL; Shipman AB; McCormick SD; Saktrakulkla P; Hornbuckle KC; Timme-Laragy AR, The emerging contaminant 3,3′-dichlorobiphenyl (PCB-11) impedes Ahr activation and Cyp1a activity to modify embryotoxicity of Ahr ligands in the zebrafish embryo model (Danio rerio). Environ. Pollut 2019, 254, 113027. [PubMed: 31421573]
104. Zhang R; Zhang X; Zhang J; Qu R; Zhang J; Liu X; Chen J; Wang Z; Yu H, Activation of avian aryl hydrocarbon receptor and inter-species sensitivity variations by polychlorinated diphenylsulfides. Environ. Sci. Technol 2014, 48, (18), 10948–10956. [PubMed: 25141271]
105. Poland A; Glover E, Comparison of 2,3,7,8-tetrachlorodibenzo-p-dioxin, a potent inducer of aryl hydrocarbon hydroxylase, with 3-methylcholanthrene. Mol. Pharmacol 1974, 10, (2), 349–59. [PubMed: 4851117]
106. Xu LC; Bresnick E, Induction of cytochrome P450IA1 in rat hepatoma cell by polycyclic hydrocarbons and a dioxin. Biochem. Pharmacol 1990, 40, (6), 1399–403. [PubMed: 2403394]
107. Hoffman TE; Acerbo ER; Carranza KF; Gilberto VS; Wallis LE; Hanneman WH, Ultrasensitivity dynamics of diverse aryl hydrocarbon receptor modulators in a hepatoma cell line. Arch. Toxicol 2019, 93, (3), 635–647. [PubMed: 30569404]
108. Harper T; Joshi AD; Elferink CJ, Identification of stanniocalcin 2 as a novel aryl hydrocarbon receptor target gene. J. Pharmacol. Exp. Ther 2013, 344, (3), 579–588. [PubMed: 23269473]
109. Lowe MM; Mold JE; Kanwar B; Huang Y; Louie A; Pollastri MP; Wang C; Patel G; Franks DG; Schlezinger J; Sherr DH; Silverstone AE; Hahn ME; McCune JM, Identification of cinnabarinic acid as a novel endogenous aryl hydrocarbon receptor ligand that drives IL-22 production. PLoS One 2014, 9, (2), e87877. [PubMed: 24498387]
110. Joshi AD; Carter DE; Harper T; Elferink CJ, Aryl hydrocarbon receptor-dependent stanniocalcin 2 induction by cinnabarinic acid provides cytoprotection against endoplasmic reticulum and oxidative stress. J. Pharmacol. Exp. Ther 2015, 353, (1), 201–212. [PubMed: 25672339]
111. Zhao B; Degroot DE; Hayashi A; He G; Denison MS, CH223191 is a ligand-selective antagonist of the Ah (Dioxin) receptor. Toxicol. Sci 2010, 117, (2), 393–403. [PubMed: 20634293]
112. Murray IA; Flaveny CA; Chiaro CR; Sharma AK; Tanos RS; Schroeder JC; Amin SG; Bisson WH; Kolluri SK; Perdew GH, Suppression of cytokine-mediated complement factor gene expression through selective activation of the Ah receptor with 3′,4′-dimethoxy-α-naphthoflavone. Mol. Pharmacol 2011, 79, (3), 508–519. [PubMed: 21127131]
113. Chen G; Konstantinov AD; Chittim BG; Joyce EM; Bols NC; Bunce NJ, Synthesis of polybrominated diphenyl ethers and their capacity to induce CYP1A by the Ah receptor mediated pathway. Environ. Sci. Technol 2001, 35, (18), 3749–3756. [PubMed: 11783655]
114. Poland A; Knutson JC, 2,3,7,8-tetrachlorodibenzo-p-dioxin and related halogenated aromatic hydrocarbons: examination of the mechanism of toxicity. Annu. Rev. Pharmacol. Toxicol 1982, 22, 517–54. [PubMed: 6282188]
115. EPA, U. In Recommended toxicity equivalence factors (TEFs) for human health risk assessments of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin and dioxin-like compounds, 2010; Risk Assessment Forum Washington, DC: 2010.
116. van Birgelen AP, Hexachlorobenzene as a possible major contributor to the dioxin activity of human milk. Environ. Health Perspect 1998, 106, (11), 683–8.

117. Hahn ME; Goldstein JA; Linko P; Gasiewicz TA, Interaction of hexachlorobenzene with the receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin in vitro and in vivo. Evidence that hexachlorobenzene is a weak Ah receptor agonist. Arch. Biochem. Biophys 1989, 270, (1), 344–55. [PubMed: 2539049]
118. Wu Y; Tan H; Zhou C; Crimmins BS; Holsen TM; Chen D, Bioaccumulation and spatiotemporal trends of polyhalogenated carbazoles in Great Lakes fish from 2004 to 2016. Environ. Sci. Technol 2018, 52, (8), 4536–4545. [PubMed: 29565583]
119. Zhang X; Qin L; Qu R; Feng M; Wei Z; Wang L; Wang Z, Occurrence of polychlorinated diphenyl sulfides (PCDPSs) in surface sediments and surface water from the Nanjing section of the Yangtze River. Environ. Sci. Technol 2014, 48, (19), 11429–11436. [PubMed: 25168171]
120. Şahin AD; Saçan MT, Understanding the toxic potencies of xenobiotics inducing TCDD/TCDF-like effects. SAR QSAR Environ. Res 2018, 29, (2), 117–131. [PubMed: 29308921]
121. Liu H; Shi L; Giesy JP; Yu H, Polychlorinated diphenyl sulfides can induce ROS and genotoxicity via the AhR-CYP1A1 pathway. Chemosphere 2019, 223, 165–170. [PubMed: 30776761]
122. Gregoraszczuk EL; Barć J; Falandysz J, Differences in the action of lower and higher chlorinated polychlorinated naphthalene (PCN) congeners on estrogen dependent breast cancer cell line viability and apoptosis, and its correlation with Ahr and CYP1A1 expression. Toxicology 2016, 366-367, 53–59. [PubMed: 27501765]
123. Klocke C; Lein PJ, Evidence implicating non-dioxin-like congeners as the key mediators of polychlorinated biphenyl (PCB) developmental neurotoxicity. Int. J. Mol. Sci 2020, 21, (3), 1013.
124. van Duursen MBM; van Ede KI; van den Berg M, One TEF concept does not fit all: The case for human risk assessment of polychlorinated biphenyls. Curr. Opin. Toxicol 2017, 2, 103–108.
125. Fang M; Guo J; Chen D; Li A; Hinton DE; Dong W, Halogenated carbazoles induce cardiotoxicity in developing zebrafish (Danio rerio) embryos. Environ. Toxicol. Chem 2016, 35, (10), 2523–2529. [PubMed: 26932193]
126. Ji C; Yue S; Gu J; Kong Y; Chen H; Yu C; Sun Z; Zhao M, 2,7-Dibromocarbazole interferes with tube formation in HUVECs by altering Ang2 promoter DNA methylation status. Sci. Total Environ 2019, 697, 134156. [PubMed: 32380619]
127. AhR Agonist Activity Confirmation of Polyhalogenated Carbazoles (PHCZs) Using an Integration of in Vitro, in Vivo, and in Silico Models. Environ. Sci. Technol 2019.
128. Zhang R; Zhang X; Shi J; Feng M; Wang X; Crump D; Zhang X, Polychlorinated Diphenyl Sulfides: An Emerging Class of Persistent, Bioaccumulative, and Toxic Substances in the Environment. Environ. Toxicol. Chem 2021, 40, (10), 2657–2666. [PubMed: 34003500]
129. Mostrag A; Puzyn T; Haranczyk M, Modeling the overall persistence and environmental mobility of sulfur-containing polychlorinated organic compounds. Environ. Sci. Pollut. Res. Int 2010, 17, (2), 470–477. [PubMed: 19937279]
130. Shi J; Zhang X; Qu R; Xu Y; Wang Z, Synthesis and QSPR study on environment-related properties of polychlorinated diphenyl sulfides (PCDPSs). Chemosphere 2012, 88, (7), 844–54. [PubMed: 22546637]
131. Li Y; Li M; Shi J; Yang X; Wang Z, Hepatic antioxidative responses to PCDPSs and estimated short-term biotoxicity in freshwater fish. Aquat. Toxicol 2012, 120-121, 90–98. [PubMed: 22640874]
132. Fang B; Shi J; Qin L; Feng M; Cheng D; Wang T; Zhang X, Toxicity evaluation of 4,4′-di-CDPS and 4,4′-di-CDE on green algae Scenedesmus obliquus: growth inhibition, change in pigment content, and oxidative stress. Environ. Sci. Pollut. Res. Int 2018, 25, (16), 15630–15640. [PubMed: 29574639]
133. Abbasi G; Buser AM; Soehl A; Murray MW; Diamond ML, Stocks and flows of PBDEs in products from use to waste in the U.S. and Canada from 1970 to 2020. Environ. Sci. Technol 2015, 49, (3), 1521–8. [PubMed: 25548829]
134. Klinčić D; Dvoršćak M; Jagić K; Mendaš G; Herceg Romanić S, Levels and distribution of polybrominated diphenyl ethers in humans and environmental compartments: a comprehensive review of the last five years of research. Environ. Sci. Pollut. Res. Int 2020, 27, (6), 5744–5758. [PubMed: 31933075]

135. Zota AR; Mitro SD; Robinson JF; Hamilton EG; Park JS; Parry E; Zoeller RT; Woodruff TJ, Polybrominated diphenyl ethers (PBDEs) and hydroxylated PBDE metabolites (OH-PBDEs) in maternal and fetal tissues, and associations with fetal cytochrome P450 gene expression. Environ. Int 2018, 112, 269–278. [PubMed: 29316516]

136. Meerts IA; Letcher RJ; Hoving S; Marsh G; Bergman A; Lemmen JG; van der Burg B; Brouwer A, In vitro estrogenicity of polybrominated diphenyl ethers, hydroxylated PDBEs, and polybrominated bisphenol A compounds. Environ. Health Perspect 2001, 109, (4), 399–407. [PubMed: 11335189]

137. Kojima H; Takeuchi S; Uramaru N; Sugihara K; Yoshida T; Kitamura S, Nuclear hormone receptor activity of polybrominated diphenyl ethers and their hydroxylated and methoxylated metabolites in transactivation assays using Chinese hamster ovary cells. Environ. Health Perspect 2009, 117, (8), 1210–8. [PubMed: 19672399]

138. Macaulay LJ; Chen A; Rock KD; Dishaw LV; Dong W; Hinton DE; Stapleton HM, Developmental toxicity of the PBDE metabolite 6-OH-BDE-47 in zebrafish and the potential role of thyroid receptor β. Aquat. Toxicol 2015, 168, 38–47. [PubMed: 26433919]

139. Dingemans MM; van den Berg M; Westerink RH, Neurotoxicity of brominated flame retardants: (in)direct effects of parent and hydroxylated polybrominated diphenyl ethers on the (developing) nervous system. Environ. Health Perspect 2011, 119, (7), 900–907. [PubMed: 21245014]

140. Yang J; Zhao H; Chan KM, Toxic effects of polybrominated diphenyl ethers (BDE 47 and 99) and localization of BDE-99-induced cyp1a mRNA in zebrafish larvae. Toxicol. Rep 2017, 4, 614–624. [PubMed: 29657921]

141. Su G; Xia J; Liu H; Lam MH; Yu H; Giesy JP; Zhang X, Dioxin-like potency of HO- and MeO-analogues of PBDEs' the potential risk through consumption of fish from eastern China. Environ. Sci. Technol 2012, 46, (19), 10781–10788. [PubMed: 22954249]

142. Gu C; Cai J; Fan X; Bian Y; Yang X; Xia Q; Sun C; Jiang X, Theoretical investigation of AhR binding property with relevant structural requirements for AhR-mediated toxicity of polybrominated diphenyl ethers. Chemosphere 2020, 249, 126554. [PubMed: 32213394]

143. Peters AK; Nijmeijer S; Gradin K; Backlund M; Bergman A; Poellinger L; Denison MS; Van den Berg M, Interactions of polybrominated diphenyl ethers with the aryl hydrocarbon receptor pathway. Toxicol. Sci 2006, 92, (1), 133–42. [PubMed: 16601081]

144. Yang J; Zhu J; Chan KM, BDE-99, but not BDE-47, is a transient aryl hydrocarbon receptor agonist in zebrafish liver cells. Toxicol. Appl. Pharmacol 2016, 305, 203–215. [PubMed: 27343407]

145. Hu W; Liu H; Sun H; Shen O; Wang X; Lam MH; Giesy JP; Zhang X; Yu H, Endocrine effects of methoxylated brominated diphenyl ethers in three in vitro models. Mar. Pollut. Bull 2011, 62, (11), 2356–2361. [PubMed: 21930287]

146. Suzuki G; Michinaka C; Matsukami H; Noma Y; Kajiwara N, Validity of using a relative potency factor approach for the risk management of dioxin-like polychlorinated naphthalenes. Chemosphere 2020, 244, 125448. [PubMed: 31812059]

147. Han Y; Liu W; Li H; Lei R; Liu G; Gao L; Su G, Distribution of polychlorinated naphthalenes (PCNs) in the whole blood of typical meat animals. J. Environ. Sci 2018, 72, 208–212.

148. Lisek M; Stragierowicz J; Guo F; Prosseda PP; Wiktorska M; Ferenc B; Kilanowicz A; Zylinska L; Boczek T, Hexachloronaphthalene induces mitochondrial-dependent neurotoxicity via a mechanism of enhanced production of reactive oxygen species. Oxid. Med. Cell Longev 2020, 2020, 2479234. [PubMed: 32685088]

149. Stragierowicz J; Bruchajzer E; Daragó A; Nasiadek M; Kilanowicz A, Hexachloronaphthalene (HxCN) as a potential endocrine disruptor in female rats. Environ. Pollut 2018, 243, (Pt B), 1026–1035. [PubMed: 30253293]

150. Li C; Zhang L; Li J; Min Y; Yang L; Zheng M; Wu Y; Yang Y; Qin L; Liu G, Polychlorinated naphthalenes in human milk: Health risk assessment to nursing infants and source analysis. Environ. Int 2020, 136, 105436. [PubMed: 31887713]

151. Zhu Q; Zhang X; Dong S; Gao L; Liu G; Zheng M, Gas and particle size distributions of polychlorinated naphthalenes in the atmosphere of Beijing, China. Environ. Pollut 2016, 212, 128–134. [PubMed: 26840526]

152. Hu W; Sorrentino C; Denison MS; Kolaja K; Fielden MR, Induction of cyp1a1 is a nonspecific biomarker of aryl hydrocarbon receptor activation: results of large scale screening of pharmaceuticals and toxicants in vivo and in vitro. Mol. Pharmacol 2007, 71, (6), 1475–1486. [PubMed: 17327465]
153. Karchner SI; Franks DG; Kennedy SW; Hahn ME, The molecular basis for differential dioxin sensitivity in birds: role of the aryl hydrocarbon receptor. PNAS 2006, 103, (16), 6252–6257. [PubMed: 16606854]
154. Poland A; Glover E; Ebetino FH; Kende AS, Photoaffinity labeling of the Ah receptor. J. Biol. Chem 1986, 261, (14), 6352–65. [PubMed: 3009454]
155. Henry EC; Bemis JC; Henry O; Kende AS; Gasiewicz TA, A potential endogenous ligand for the aryl hydrocarbon receptor has potent agonist activity in vitro and in vivo. Arch. Biochem. Biophys 2006, 450, (1), 67–77. [PubMed: 16545771]
156. Opitz CA; Litzenburger UM; Sahm F; Ott M; Tritschler I; Trump S; Schumacher T; Jestaedt L; Schrenk D; Weller M; Jugold M; Guillemin GJ; Miller CL; Lutz C; Radlwimmer B; Lehmann I; von Deimling A; Wick W; Platten M, An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. Nature 2011, 478, (7368), 197–203. [PubMed: 21976023]
157. Karchner SI; Powell WH; Hahn ME, Identification and functional characterization of two highly divergent aryl hydrocarbon receptors (AHR1 and AHR2) in the teleost Fundulus heteroclitus. J. Biol. Chem 1999, 274, (47), 33814–33824. [PubMed: 10559277]
158. Poland A; Glover E, Variation in the molecular mass of the Ah receptor among vertebrate species and strains of rats. Biochem. Biophys. Res. Commun 1987, 146, (3), 1439–49. [PubMed: 3040002]
159. Hahn ME; Poland A; Glover E; Stegeman JJ, Photoaffinity labeling of the Ah receptor: phylogenetic survey of diverse vertebrate and invertebrate species. Arch. Biochem. Biophys 1994, 310, (1), 218–28. [PubMed: 8161208]
160. Bradfield CA; Poland A, A competitive binding assay for 2,3,7,8-tetrachlorodibenzo-p-dioxin and related ligands of the Ah receptor. Mol. Pharmacol 1988, 34, (5), 682–8. [PubMed: 2848187]
161. Poland A; Palen D; Glover E, Analysis of the four alleles of the murine aryl hydrocarbon receptor. Mol. Pharmacol 1994, 46, (5), 915–21. [PubMed: 7969080]
162. Ema M; Ohe N; Suzuki M; Mimura J; Sogawa K; Ikawa S; Fujii-Kuriyama Y, Dioxin binding activities of polymorphic forms of mouse and human arylhydrocarbon receptors. J. Biol. Chem 1994, 269, (44), 27337–43. [PubMed: 7961644]
163. Mahiout S; Lindén J; Esteban J; Sánchez-Pérez I; Sankari S; Pettersson L; Håkansson H; Pohjanvirta R, Toxicological characterisation of two novel selective aryl hydrocarbon receptor modulators in Sprague-Dawley rats. Toxicol. Appl. Pharmacol 2017, 326, 54–65. [PubMed: 28433708]
164. Pohjanvirta R; Korkalainen M; McGuire J; Simanainen U; Juvonen R; Tuomisto JT; Unkila M; Viluksela M; Bergman J; Poellinger L; Tuomisto J, Comparison of acute toxicities of indolo[3,2-b]carbazole (ICZ) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in TCDD-sensitive rats. Food Chem. Toxicol 2002, 40, (7), 1023–32. [PubMed: 12065225]
165. Elad T; Belkin S, Reporter Gene Assays in Ecotoxicology. Adv. Biochem. Eng. Biotechnol 2017, 157, 135–157. [PubMed: 27928578]
166. Struss AK; Pasini P; Daunert S, Biosensing systems based on genetically engineered whole cells. In Recognition Receptors in Biosensors, Zourob M, Ed. Springer New York: New York, NY, 2010; pp 565–598.
167. Ding G; Wang L; Zhang S; Li S; Xie Q; Xu L; Zhou Z; He Y; Zhao B, Simple and rapid determination of dioxin in fish and sea food using a highly sensitive reporter cell line, CBG 2.8D. J. Environ. Sci 2021, 100, 353–359.
168. Hayashi A; Denison MS, Development of a novel recombinant cell line for detection and characterization of Ah receptor nuclear translocation in intact cells. Toxicol. In Vitro 2020, 66, 104873. [PubMed: 32333947]
169. Lin CI; Hsieh CH; Lee SS; Lee WS; Chang-Chien GP; Pan CY; Lee H, Establishment of a fluorescence resonance energy transfer-based bioassay for detecting dioxin-like compounds. J. Biomed. Sci 2008, 15, (6), 833–840. [PubMed: 18604597]

170. Csanaky IL; Lickteig AJ; Klaassen CD, Aryl hydrocarbon receptor (AhR) mediated short-term effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on bile acid homeostasis in mice. Toxicol. Appl. Pharmacol 2018, 343, 48–61. [PubMed: 29452137]

171. Phadnis-Moghe AS; Chen W; Li J; Crawford RB; Bach A; D'Ingillo S; Kovalova N; Suarez-Martinez JE; Kaplan BL; Harrill JA; Budinsky R; Rowlands JC; Thomas RS; Kaminski NE, Immunological characterization of the aryl hydrocarbon receptor (AHR) knockout rat in the presence and absence of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicology 2016, 368-369, 172–182. [PubMed: 27590929]

172. Zhang R; Wang X; Zhang X; Song C; Letcher RJ; Liu C, Polychlorinated diphenylsulfides activate aryl hydrocarbon receptor 2 in zebrafish embryos: potential mechanism of developmental toxicity. Environ. Sci. Technol 2018, 52, (7), 4402–4412. [PubMed: 29522672]

173. Zhang X; Xia P; Wang P; Yang J; Baird DJ, Omics advances in ecotoxicology. Environ. Sci. Technol 2018, 52, (7), 3842–3851. [PubMed: 29481739]

174. Shankar P; Geier MC; Truong L; McClure RS; Pande P; Waters KM; Tanguay RL, Coupling genome-wide transcriptomics and developmental toxicity profiles in zebrafish to characterize polycyclic aromatic hydrocarbon (PAH) hazard. Int. J. Mol. Sci 2019, 20, (10), 2570.

175. Xia P; Zhang H; Peng Y; Shi W; Zhang X, Pathway-based assessment of single chemicals and mixtures by a high-throughput transcriptomics approach. Environ. Int 2020, 136, 105455. [PubMed: 31945694]

176. Zhang J; Zhang C; Du Z; Zhu L; Wang J; Wang J; Li B, Emerging contaminant 1,3,6,8-tetrabromocarbazole induces oxidative damage and apoptosis during the embryonic development of zebrafish (Danio rerio). Sci. Total Environ 2020, 743, 140753. [PubMed: 32758839]

177. Zhang R; Wang X; Zhang X; Zhang J; Zhang X; Shi X; Crump D; Letcher RJ; Giesy JP; Liu C, Down-regulation of hspb9 and hspb11 contributes to wavy notochord in zebrafish embryos following exposure to polychlorinated diphenylsulfides. Environ. Sci. Technol 2018, 52, (21), 12829–12840. [PubMed: 30335980]

178. Zhang X; Liu F; Chen B; Li Y; Wang Z, Acute and subacute oral toxicity of polychlorinated diphenyl sulfides in mice: determining LD50 and assessing the status of hepatic oxidative stress. Environ. Toxicol. Chem 2012, 31, (7), 1485–1493. [PubMed: 22549922]

179. Peters AK; Sanderson JT; Bergman A; van den Berg M, Antagonism of TCDD-induced ethoxyresorufin-O-deethylation activity by polybrominated diphenyl ethers (PBDEs) in primary cynomolgus monkey (Macaca fascicularis) hepatocytes. Toxicol. Lett 2006, 164, (2), 123–132. [PubMed: 16448790]

180. Koike E; Yanagisawa R; Takigami H; Takano H, Penta- and octa-bromodiphenyl ethers promote proinflammatory protein expression in human bronchial epithelial cells in vitro. Toxicol. In Vitro 2014, 28, (2), 327–333. [PubMed: 24184330]

181. Kuiper RV; Bergman A; Vos JG; van den Berg M, Some polybrominated diphenyl ether (PBDE) flame retardants with wide environmental distribution inhibit TCDD-induced EROD activity in primary cultured carp (Cyprinus carpio) hepatocytes. Aquat. Toxicol 2004, 68, (2), 129–139. [PubMed: 15145223]

182. Wahl M; Guenther R; Yang L; Bergman A; Straehle U; Strack S; Weiss C, Polybrominated diphenyl ethers and arylhydrocarbon receptor agonists: Different toxicity and target gene expression. Toxicol. Lett 2010, 198, (2), 119–126. [PubMed: 20566336]

183. Glazer L; Wells CN; Drastal M; Odamah KA; Galat RE; Behl M; Levin ED, Developmental exposure to low concentrations of two brominated flame retardants, BDE-47 and BDE-99, causes life-long behavioral alterations in zebrafish. Neurotoxicology 2018, 66, 221–232. [PubMed: 28935585]

184. Cao L; Zheng Z; Ren XM; Andersson PL; Guo L, Structure-dependent activity of polybrominated diphenyl ethers and their hydroxylated metabolites on estrogen related receptor γ: in vitro and in silico study. Environ. Sci. Technol 2018, 52, (15), 8894–8902. [PubMed: 30005570]

185. Zhang R; Zhang J; Zhang X; Zhang J; Su G; Farmahin R; Giesy JP; Yu H, In vitro dioxin-like potencies of HO- and MeO-PBDEs and inter-species sensitivity variation in birds. Ecotoxicol. Environ. Saf 2016, 126, 202–210. [PubMed: 26771532]

186. Cao L; Ren X; Yang Y; Wan B; Guo L; Chen D; Fan Y, Hydroxylated polybrominated diphenyl ethers exert estrogenic effects via non-genomic g protein-coupled estrogen receptor mediated pathways. Environ. Health Perspect 2018, 126, (5), 057005. [PubMed: 29790728]

187. Cantón RF; Scholten DE; Marsh G; de Jong PC; van den Berg M, Inhibition of human placental aromatase activity by hydroxylated polybrominated diphenyl ethers (OH-PBDEs). Toxicol. Appl. Pharmacol 2008, 227, (1), 68–75. [PubMed: 18022659]

188. Legradi J; Pomeren MV; Dahlberg AK; Legler J, Effects of hydroxylated polybrominated diphenyl ethers in developing zebrafish are indicative of disruption of oxidative phosphorylation. Int. J. Mol. Sci 2017, 18, (5), 970.

189. Liu Y; Guo R; Tang S; Zhu F; Zhang S; Yan Z; Chen J, Single and mixture toxicities of BDE-47, 6-OH-BDE-47 and 6-MeO-BDE-47 on the feeding activity of Daphnia magna: From behavior assessment to neurotoxicity. Chemosphere 2018, 195, 542–550. [PubMed: 29277034]

190. Xu X; Huang H; Wen B; Wang S; Zhang S, Phytotoxicity of brominated diphenyl ether-47 (BDE-47) and its hydroxylated and methoxylated analogues (6-OH-BDE-47 and 6-MeO-BDE-47) to maize (Zea mays L.). Chem. Res. Toxicol 2015, 28, (3), 510–517. [PubMed: 25654621]

191. Villeneuve DL; Kannan K; Khim JS; Falandysz J; Nikiforov VA; Blankenship AL; Giesy JP, Relative potencies of individual polychlorinated naphthalenes to induce dioxin-like responses in fish and mammalian in vitro bioassays. Arch. Environ. Contam. Toxicol 2000, 39, (3), 273–281. [PubMed: 10948276]

192. Barć J; Gregoraszczuk E, Effects of individual polychlorinated naphthalene (PCN) components of Halowax 1051 and two defined, artificial PCN mixtures on AHR and CYP1A1 protein expression, steroid secretion and expression of enzymes involved in steroidogenesis (CYP17, 17β-HSD and CYP19) in porcine ovarian follicles. Toxicology 2014, 322, 14–22. [PubMed: 24810611]

193. Kilanowicz A; Czekaj P; Sapota A; Skrzypinska-Gawrysiak M; Bruchajzer E; Darago A; Czech E; Plewka D; Wiaderkiewicz A; Sitarek K, Developmental toxicity of hexachloronaphthalene in Wistar rats. A role of CYP1A1 expression. Reprod. Toxicol 2015, 58, 93–103. [PubMed: 26403959]

194. Omura M; Masuda Y; Hirata M; Tanaka A; Makita Y; Ogata R; Inoue N, Onset of spermatogenesis is accelerated by gestational administration of 1,2,3,4,6,7-hexachlorinated naphthalene in male rat offspring. Environ. Health Perspect 2000, 108, (6), 539–44. [PubMed: 10856028]

195. Blankenship AL; Kannan K; Villalobos SA; Villeneuve DL; Falandysz J; Imagawa T; Jakobsson E; Giesy JP, Relative potencies of individual polychlorinated naphthalenes and halowax mixtures to induce ah receptor-mediated responses. Environ. Sci. Technol 2000, 34, (15), 3153–3158.

196. Vinitskaya H; Lachowicz A; Kilanowicz A; Bartkowiak J; Zylinska L, Exposure to polychlorinated naphthalenes affects GABA-metabolizing enzymes in rat brain. Environ. Toxicol. Pharmacol 2005, 20, (3), 450–455. [PubMed: 21783625]

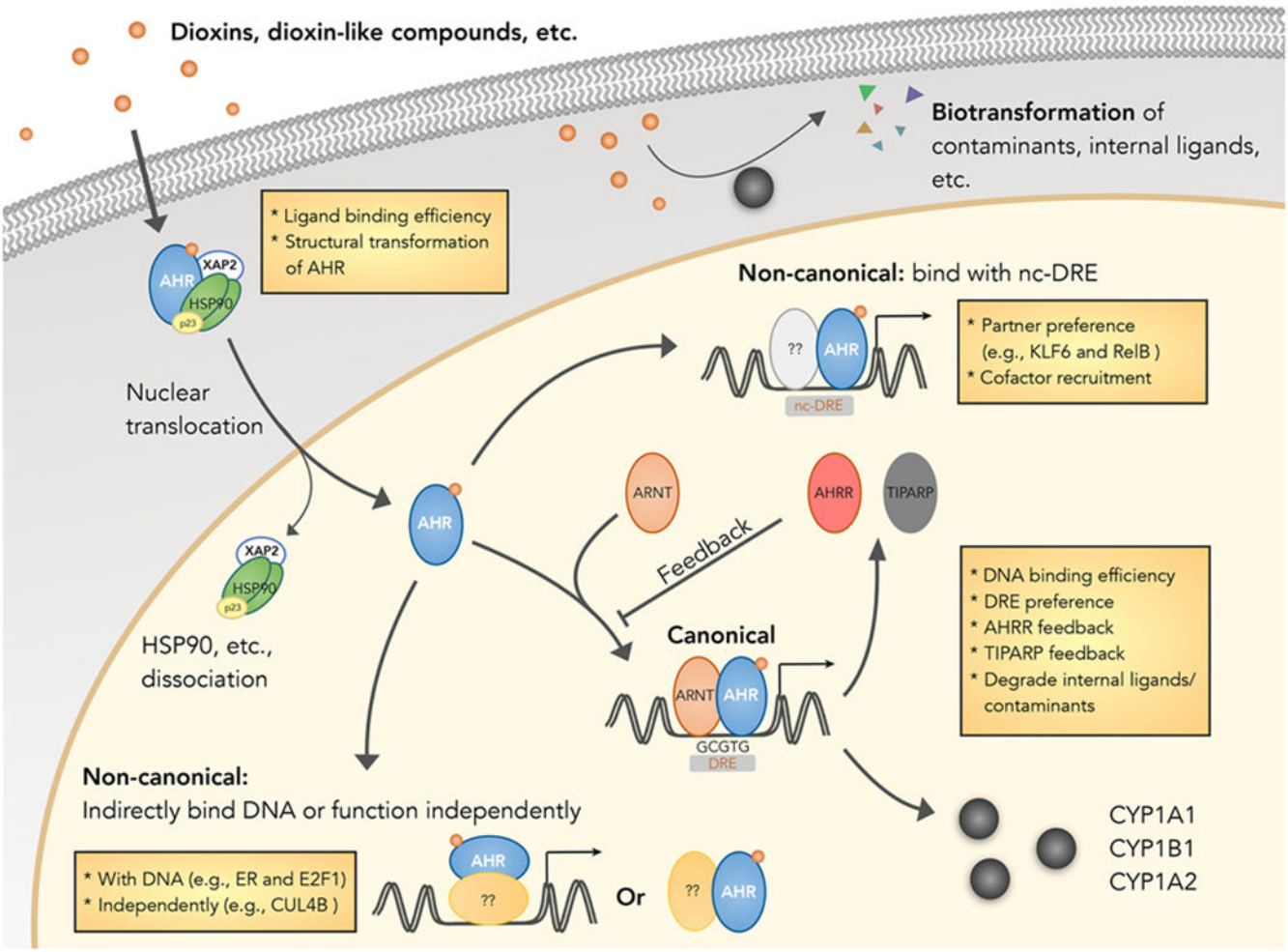


Figure 1.

Mechanisms of ligand-dependent AHR activation and AHR-mediated activities with the key influencing factors marked in the boxes. Once potent ligands (including dioxins and DLCs) enter the cell, they bind AHR to induce AHR nuclear translocation, partner dissociation, and the canonical response of AHR-DRE association as well as target gene expression. Alternatively, AHR can exert non-canonical signaling by indirectly binding DNA or functioning with other proteins.

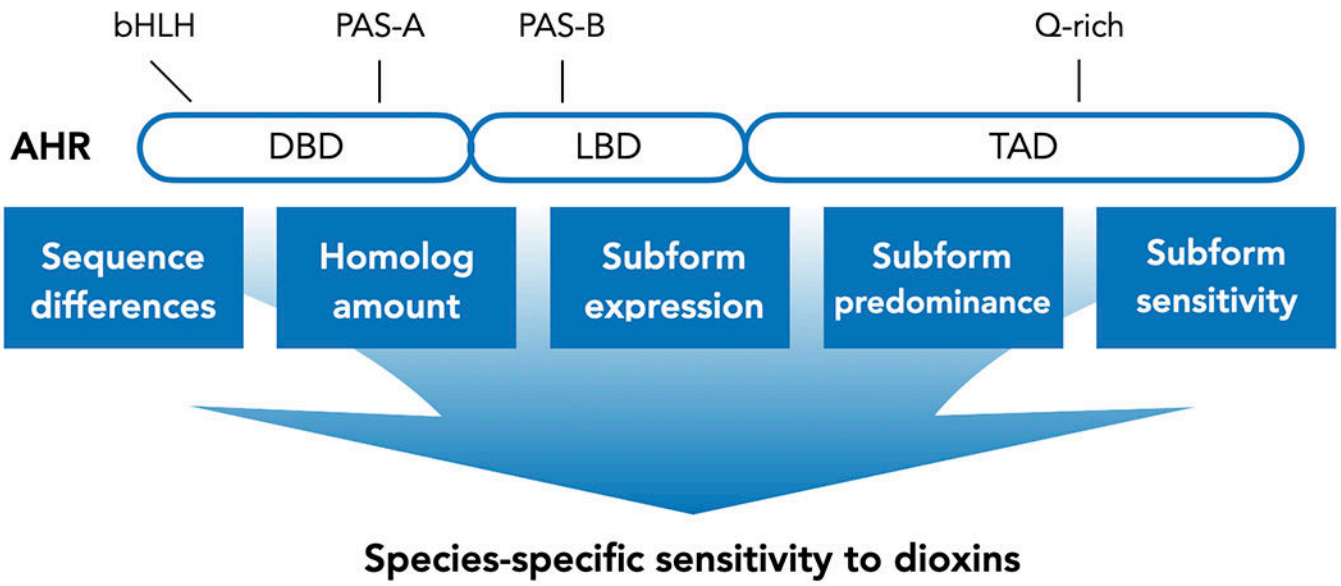
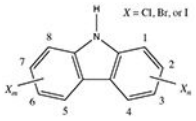
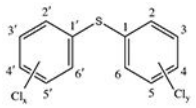
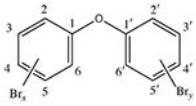
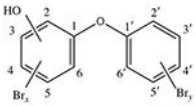
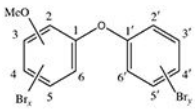
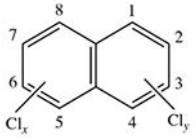


Figure 2.

Key factors that affect species-specific sensitivity to dioxins and DLCs, including the sequence differences of AHRs, the number of homologs in different species and properties of subforms (expression abundance, functional predominance, and sensitivity).

Table 1.

Structure, potency, and toxicity of the DLCs of PHCZs, PCDPSs, PBDEs (and analogs), and PCNs.

Compounds	Structure	Potency and toxicity	
		Potency relative to TCDD	***In vivo/vitro toxicity***
PHCZs		1.3×10^{-5} to 6.6×10^{-4} (human *CYP1A1*)[45]	cardiotoxicity (zebrafish)[125]
		1.3×10^{-4} to 9.7×10^{-3} (human *CYP1B1*)[45]	endocrine disturbance (zebrafish)[13]
		NE to 2×10^{-2} (CBG 2.8D cells)[14]	oxidative damage and apoptosis (zebrafish embryo)[176]
			inhibited tube formation (HUVECs)[126]
PCDPSs		NE to 7.4×10^{-4} (chicken AHR)[104]	induce ROS and genotoxicity (HepG2 cells)[121]
		NE to 1.5×10^{-2} (pheasant AHR)[104]	notochord kinks and twists (zebrafish)[177]
		NE to 2.1×10^{-1} (quail AHR)[104]	hepatic oxidative stress (mouse)[178]
			alter antioxidant enzymes (goldfish) [131]
			growth inhibition (*Scenedesmus obliquus*)[132]
PBDEs		No statistically significant induction of CYP1A (monkey hepatocytes)[179]	promote proinflammatory protein (zebrafish)[180]
		inhibit TCDD-induced EROD activity (primary cultured carp hepatocytes)[181]	malformation (zebrafish embryo)[182]
		BDE-99 as a transient AHR agonist (ZFL cells)	life-long behavioral alterations (zebrafish)[183]
			bind and activate ERRγ (HeLa cells)[184]
OH-PBDEs		NE to 7.8×10^{-4} (chicken AHR)[185]	affect early life development (zebrafish)[138]
		NE to 1.1×10^{-2} (pheasant AHR)[185]	estrogenic effects via GPER (SKBR3 cells)[186]
		NE to 1.7×10^{-1} (quail AHR)[185]	inhibit human placental aromatase activity[187]
		7.35×10^{-12} to 4×10^{-4} (H4IIE-*luc*)[141]	disrupt oxidative phosphorylation (zebrafish larvae)[188]
MeO-PBDEs		NE to 1.7×10^{-4} (chicken AHR)[185]	depressive effect on feeding behavior (*Daphnia magna*)[189]
		NE to 3.7×10^{-3} (pheasant AHR)[185]	phytotoxicity (Maize)[190]
		NE to 6.4×10^{-2} (quail AHR)[185]	endocrine disruption (CHO cells)[137]
		2.23×10^{-8} to 6.48×10^{-5} (H4IIE-*luc*)[141]	
PCNs		3.6×10^{-10} to 2.6×10^{-3} (H4IIE-EROD)[191]	androgenic effects (ovarian follicles)[192]
		1.0×10^{-8} to 2.2×10^{-8} (H4IIE-*luc*)[191]	embryo- and feto-toxic effects (rats)[193]
		1.6×10^{-7} to 3.1×10^{-3} (PLHC-1 cells)[191]	accelerate spermatogenesis (rat)[194]
		1.5×10^{-4} to 4.0×10^{-3} (H4IIE-*luc*)[195]	disturb GABA metabolism (rat brain)[196]

NE: not estimated

*Note that the potency ranges listed here are determined by the original research using some of the selected congeners but not all.