Chapter 11

Aquatic Toxicity of Dioxins and Related Chemicals

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1. GENERAL TOXICOLOGICAL CHARACTERISTICS

Polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and biphenyls (PCBs) belong to a family of lipophilic halogenated aromatic hydrocarbons that have similar structures, resist chemical and biological degradation, and persist in the environment posing a potential risk to fish, wildlife, and human health. There are more than 400 possible polychlorinated dioxins, dibenzofuran, and biphenyl congeners; however, only 21 are considered highly toxic.\(^1,2\) The more potent congeners are planar or coplanar molecules with lateral chlorine substitutions, approximate isostereomers of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the most potent PCDD, PCDF, or PCB congener.\(^3\) In mammals, TCDD and TCDD-like dioxin, dibenzofuran, and biphenyl congeners evoke similar patterns of toxic responses within a given species, and share a common mechanism of action mediated by binding the cellular aryl hydrocarbon (Ah) receptor and altering gene transcription.\(^3,4\) The ability of TCDD and TCDD-like congeners to produce toxicity in mammalian species correlates with their Ah receptor binding affinity and their ability to induce cytochrome P450IA enzyme activity, a gene subfamily that catalyzes monoxygenase reactions and whose expression is regulated by the Ah receptor.\(^4-6\)
1.1. Toxicological Characteristics in Fish

Certain lines of evidence suggest that TCDD and TCDD-like PCDD, PCDF, and PCB congeners may also manifest toxicity in fish via an Ah receptor-mediated mechanism.

1.1.1. Presence of the Ah Receptor and P450IA1 Inducibility

The ability of mammalian Ah receptor agonists to induce hepatic cytochrome P450IA1 activity in a variety of fish species correlates with the presence of the Ah receptor in those species. The Ah receptor has been detected in advanced classes of fish, including two species of elasmobranchs, smooth dogfish (*Mustelus canis*) and spiny dogfish (*Squalus acanthias*); and five species of teleosts, scup (*Stenotomus chrysops*),7 winter flounder (*Pseudopleuronectes americanus*),7 killifish (*Fundulus heteroclitus*),7 rainbow trout (*Oncorhynchus mykiss*),7,8 and brown trout (*Salmo trutta*),7 but has not been detected in Atlantic hagfish (*Myxine glutinosa*)7 or sea lamprey (*Petromyzon marinus*),7 species belonging to a primitive class of jawless aquatic vertebrates, the agnathans. TCDD or other mammalian Ah receptor agonists induced hepatic cytochrome P450IA1 activity in the seven fish species in which the Ah receptor was detected,7–13 but these same receptor agonists did not induce P450IA1 activity in hagfish or sea lamprey, the two species in which the Ah receptor was not detected.7·14 Although the assay methods used may not be suitable for detecting the Ah receptor in hagfish and sea lamprey, the inability of Ah receptor agonists to induce P450IA1 enzyme activity in these species strongly suggests that the Ah receptor is not present in hagfish or sea lamprey, and that in fish, as in birds and mammals, Ah receptor binding is required for P450IA1 induction.

The Ah receptor has also been detected in fish cells in culture including RTH-149 rainbow trout hepatoma cells,15 PLHC-1 desert topminnow (*Poeciliopsis lucida*) hepatoma cells,7 and RTG-2 rainbow trout embryonic gonad cells.16 Mammalian Ah receptor agonists induced cytochrome P450IA1 activity in both hepatoma cell lines,7,15 and competitively bound to the putative Ah receptor in RTG-2 embryonic gonad cells with a rank order of agonist affinity identical to that for the murine Ah receptor.16

1.1.2. Characterization of the Fish Ah Receptor

In mammals the Ah receptor is a ligand-dependent, DNA-binding protein. Following specific binding of the ligand to the Ah receptor, the ligand–receptor complex binds to specific DNA sequences termed dioxin-responsive enhancers (DREs).17 DREs are adjacent to genes, such as cytochrome P450IA1, whose transcription is regulated by Ah receptor ligands, such as TCDD. Recent evidence has shown that following specific binding of TCDD to the putative hepatic Ah receptor in rainbow trout and killifish, the ligand–receptor complex can bind an oligonucleotide sequence containing a DRE upstream of the mouse cytochrome P450IA1 gene.18 This finding suggests that