Document No. 3

Handbook of
ECOTOXICOLOGY
Second Edition

Edited by
David J. Hoffman
Barnett A. Rattner
G. Allen Burton, Jr.
John Cairns, Jr.

LEWIS PUBLISHERS

A CRC Press Company
Boca Raton London New York Washington, D.C.

Cover photograph of the California red-legged frog courtesy of Gary Fellers, U.S. Geological Survey.

Cover photograph of the American alligator courtesy of Heath Rauschenberger, U.S. Geological Survey.

Library of Congress Cataloging-in-Publication Data

Handbook of ecotoxicology / David J. Hoffman ... [et al.] — 2nd ed.
p. cm.
Includes bibliographical references and index.
ISBN 1-56670-546-0 (alk. paper)
1. Environmental toxicology. I. Hoffman, David J. (David John), 1944-

RA1226 .H36 2002
615.9'02—dc21 2002075228

Visit the CRC Press Web site at www.crcpress.com

International Standard Book Number 1-56670-546-0
Library of Congress Card Number 2002075228
Printed in the United States of America 1 2 3 4 5 6 7 8 9 0
Printed on acid-free paper

CHAPTER 18

Sources, Pathways, and Effects of PCBs, Dioxins, and Dibenzofurans

Clifford P. Rice, Patrick W. O'Keefe, and Timothy J. Kubiak

CONTENTS

18.1 INTRODUCTION

Polychlorinated biphenyls (PCBs), dioxins (PCDDs), and dibenzofurans (PCDFs) all belong to a general class of pollutants labeled polyhalogenated organics. They all share the common distinction of having a benzene backbone that has chlorine substituted on it, and they all have several similarities in their modes of action, environmental pathways, and occurrence as direct products of commerce as opposed to agriculture. Bioconcentration and biomagnification are these compounds' prominent routes of exposure. The atmosphere plays an important role in the transport and fate of these compounds. Each grouping (PCBs and PCDDs/PCDFs) will be dealt with separately under each of the following major headings: Sources and Pathways in the Environment (Sections 18.2 and 18.3), Ambient Levels (Sections 18.4 and 18.5), and Effects (Section 18.6).

18.1.1 PCBs

Effective July 1979, the final PCB ban rule was implemented by the U.S. Environmental Protection Agency (EPA), which prohibited the manufacture, processing, distribution in commerce, and use of PCBs except in a totally enclosed system or unless specifically exempted by the EPA.[1] Essentially, the use of PCBs was unabated from their entry in the marketplace in the late 1920s until the early 1970s, when evidence became available that chronic exposure could result in hazard to humans and the environment. The Yusho incident[2] in Japan, in which over 1000 individuals were severely exposed to PCB-contaminated rice oil in 1968, provided a strong impetus to finalize this ban. The total worldwide production through 1976 is estimated to be about 6.1×10^{11} g[3], of which about 5.7×10^{11} g (93%, 1.25 billion lbs) were produced by Monsanto in the United States. As concern continued to mount through the 1970s, the timing was right for PCBs to become a focus of the new U.S. Toxic Substances Control Act (TSCA), which was formulated in 1976 and pursuant to which all further manufacture of PCBs by U.S. companies was banned as of 1977.

The common names for PCB varied from country to country. In the United States they were called Aroclors, in France, Phenechlor, in Japan, Kaneclor, and in Russia, Sovol.[4] PCB is the acronym for polychlorinated biphenyl. This name accurately depicts its chemical structure. Biphenyl is a compound consisting of two benzene (phenyl) rings connected by a single carbon-to-carbon bond. The polychlorinated modifier signifies that there is at least one or several chlorine atoms substituted at one or more of the ten carbons of the biphenyl backbone. The substitution of chlorine

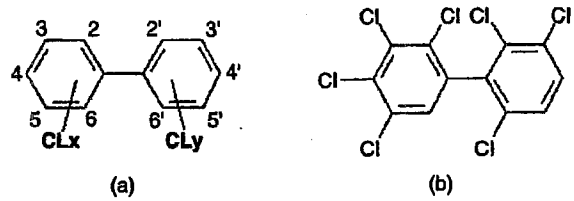

Figure 18.1 Chemical structures for PCB. (a) PCB congener numbering protocol; (b) congener, designated as BZ# 174, which is a congener that exists as two chiral forms (atropisomers, see text).

Table 18.1 Distribution of PCB Congeners ($C_{12}H_{10-n}Cl_n$)

Homolog Grouping (Based on Chlorine No.)	Possible Congeners
Monochloro-	3
Dichloro-	12
Trichloro-	24
Tetrachloro-	42
Pentachloro-	46
Hexachloro-	42
Heptachloro-	24
Octachloro-	12
Nonochloro-	3
Decachloro-	1
TOTAL	209

on the biphenyl backbone leads to the nomenclature that is typical for the more than 100 congeners that are widely described in the literature (Figure 18.1).

There are actually 209 congeners that are theoretically possible from the base structure (Figure 18.1[a], Table 18.1). The congeners are designated individually with separate BZ numbers that were assigned by Ballschmitter and Zell in 1978.[5] These congener assignments are broadly accepted today with only slight modification by the International Union of Pure and Applied Chemists.[6]

Of the possible 209 compounds, only about 100 to 150 are represented in formulations that have been used and are now widely dispersed in the environment. Besides the great numbers of different chemistries resulting from the varying chlorine substitutions (amounts and positions) that are shown in Table 18.1, there are also configurational variations, or atropisomers, within selected single congeners (nine unique pairs are possible). These configurational differences occur because of restricted rotations of the two phenyl groups when three or more *ortho*-substituted (two or six positions) chlorines are present. Each of the congeners having this property therefore exists in an enatiomeric pair. A prominent example of one of these atropisomers is BZ# 174 (Figure 18.1[b]). As they were synthesized, commercial PCBs had equal quantities of each member of the pair of these atropisomers; however, biological processes will usually degrade one form in preference to the other. Environmental chemists have begun to use measurements of PCB atropisomers in attempts to distinguish chemical from biological processing and to track environmental weathering.[7,8,9]

18.1.2 PCDDs and PCDFs

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are two related classes of aromatic heterocyclic compounds (Figure 18.2). In contrast to PCBs, PCDFs and PCDDs have no commercial use and are released into the environment as contaminants of chemical and combustion processes. The number of chlorine atoms can vary between one and eight, which allows for 75 PCDD and 135 PCDF positional isomers, respectively. The toxicity of PCDD/PCDF compounds is associated with substitution at the lateral (2,3,7, and 8) positions, and

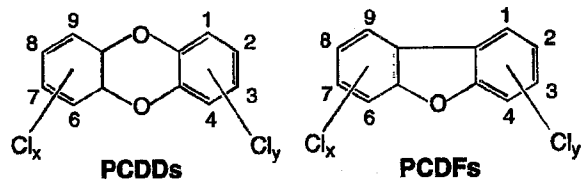

Figure 18.2 Generalized structures for PCDDs and PCDFs.

the two compounds with all of these positions occupied — 2,3,7,8-TCDD and 2,3,7,8-TCDF — are extremely toxic to certain species of laboratory animals, particularly guinea pigs (LD_{50} approx. 1 μg/kg).[10] However, other species are considerably less sensitive to the two compounds, and consequently there is no clear consensus in the scientific community on the human toxicity of PCDD/PCDF compounds.[11]

PCDD\PCDF compounds are thermally very stable, and extensive decomposition of 2,3,7,8-TCDD, the most toxic PCDD/PCDF compound, does not occur until temperatures exceed 750°C.[12] However, PCDDs and PCDFs do undergo electrophilic substitution reactions,[13] and photochemical degradation occurs in both organic solvents[14] and water.[15] In the gas phase, reactions can occur between photochemically generated hydroxyl (OH) radicals and PCDDs/PCDFs.[16] Since atmospheric PCDDs/PCDFs with six or fewer chlorines exist primarily in the vapor phase, the OH radical reactions could reduce the atmospheric concentrations of all PCDDs/PCDFs except for the hepta- and octaisomers. The 2,3,7,8-TCDD isomer has very low solubility in water, with a value of 20 ng/g reported for dissolution from a thin film,[17] and 483 ng/g reported from generator column studies.[18] As a consequence of its low water solubility, 2,3,7,8-TCDD has a very high carbon-based sediment partition coefficient, with a log K_{oc} value near 7.[19]

18.2 SOURCES AND PATHWAYS OF PCBS IN THE ENVIRONMENT

Important concerns for PCBs are their extensive release to the environment and their aquatic and terrestrial fates after release. PCBs are distributed throughout the world, a fact largely resulting from their considerable aquatic and atmospheric mobility. There is a great deal of literature on the environmental fate and properties of PCBs, including numerous books and special reports.[4,20-26] Much of the concern about this group of chemicals arises from their extensive environmental occurrence and from numerous data indicating that members of this group of compounds may be carcinogenic[27] or may cause adverse endocrine and general reproductive effects.[28]

Manufacturing sites that made extended use of the Aroclors as hydraulic fluids or that used them to manufacture electrical devices, especially transformers or fluorescent light ballasts, became the most common sites for environmental buildup. For example, die-casting equipment used great quantities of hydraulic fluids in the pressing out of metal parts for automobiles and related industries. Also, the electrical industries, especially those assembling capacitors and transformers, employed large amounts of the Aroclors as an insulating fluid. Therefore, areas where these facilities occurred, e.g., the Northeast and heavy manufacturing regions in Michigan, Wisconsin, and Illinois, became regions for major PCB buildup. Examples of documented hotspots are the General Electric Plant in Glens Falls, NY;[29] a die-casting operation on the North Branch of the Shiawasee River;[30] electronic manufacturing facilities in New Bedford Harbor;[31] and an automobile foundry and an aluminum manufacturing plant on the St. Lawrence River.[32] There also were specialized uses for PCBs that led to localized buildups. One of these uses was for carbonless paper, and buildups occurred at locations where these papers were deinked and recycled for reuse, e.g., Kalamazoo River, Kalamazoo, MI had several plants in the city and downstream,[33] and there were also plants along the lower Fox River in Wisconsin.[34] As further evidence for this manufacturing localization

for PCB contamination, it is noteworthy that even 20 years after cessation of their use, these same areas are now recognized as regions for PCB fishing advisories across the United States[35] — the Northeast, the upper Midwest, and coastal regions near population centers.

With the 1979 U.S. ban, it can now be safely said that most direct sources of PCB releases to surface waters and air have ceased, except for the occasional spills or the increasingly less frequent acts of illegal disposal or dumping.

18.2.1 Release of PCBs into the Environment

The primary emission of PCBs into the environment occurs through release to water, with maximum wildlife and human exposure occurring directly or indirectly through aqueous systems. Atmospheric processes are secondary in terms of immediate exposure, even though geographic dispersion through the atmosphere is most likely greater.

18.2.1.1 Emission of PCBs into Water

Past discharge into rivers and streams has led to significant dispersion of, and exposure to, PCBs. Fortunately, however, most of these direct discharges have ceased, and exposures in aquatic systems generally center around past deposits that reside in sediments. Many of the sites identified in the Great Lakes as "areas of concern" by the U.S./Canadian Great Lakes Water Quality Agreement[36] have this designation because of PCB buildup in their sediments (more than 70% of the 42 sites). Considerable debate continues on the relative merits/costs of dredging these and other areas to reduce exposure from these deposits. Two notable examples of high sediment buildup of PCBs are the Hudson River[37] and New Bedford Harbor.[38] The high level of PCBs in the sediment of the Upper Hudson River site remains from earlier industrial practices that, at the time, were considered acceptable.[39] There are several case studies that could be presented to describe the environmental fate and distribution of PCBs in aqueous systems. One of the most extensively documented is indeed the Hudson River PCB problem.[39,40] Among areas, the PCB spill in Duwamish Harbor in Seattle is of historical interest, as it has long since been corrected.[41] Another more recent focus is an effort underway[42] to define the extent of PCB contamination in Baltimore Harbor.

Some areas have undergone dredging as a mitigative strategy, with sampling built in as a check for improvement in the systems.[30,43] New Bedford Harbor is an estuary severely contaminated with PCBs. It has undergone a multistage Superfund remediation involving a long-term monitoring program. Based on this monitoring, it was found that the major redistributions of contaminated sediments were confined to the immediate vicinity of remedial activities; however, there was evidence that low-molecular-weight PCBs were transported farther.[34,44] In another study by Bremle and co-workers,[45] in which suction dredging was performed on a small Swedish lake, it was determined that 97% of the PCB-contaminated sediment was removed, and little excess PCB was released as a result of the dredging. This may have been aided by the use of a geotextile silt curtain that reduced leakage of PCB to the river downstream. In the early assessment process to determine options to remediate the PCB buildup in the Hudson River, separate sediment transport and resuspension studies were carried out to determine the degree of remobilization of PCBs that might take place during dredging (Toffiemire 1984, as cited in Final Environmental Impact Statement on the Hudson River PCB Reclamation Demonstration Project[46]). Losses were found to be negligible.

18.2.1.2 Emissions of PCBs into the Atmosphere

While the quantities mobilized through the air are likely similar to losses to aqueous systems, dispersion and dilution into the atmosphere are much more extensive and rapid. The impacts from air dispersion, however, are less obvious than in the aqueous situation. Atmospheric processes are clearly responsible for significant dispersion of PCBs to large isolated waterbodies like the Great

Lakes,[47-50] Lake Baikal,[51,52] and most of the marine portions of the Arctic.[53,54] Furthermore, it has been repeatedly documented that there is a general trend of atmospheric movement of the more volatile components of the Aroclor mixes to colder areas of the world.[55]

Rather than atmospheric emissions emitting directly from source areas, as was the case in the 1960s and 1970s, today's atmospheric levels originate predominantly from recycling of past atmospheric deposits. This recycling tends to maintain higher concentrations in these areas, preventing levels from declining as quickly as was observed right after sources were cut off in the late 1960s.[56] Studies of current atmospheric emission have concluded that reprocessing of soil-sorbed PCBs is a major contributor to loading in urban/industrial areas. Local hot spots will also contribute to these loads; however, estimates using known hot spots vs. general recycling have been carried out in London, and these hot-spot contributions were determined to be rather insignificant.[57]

Indoor levels of PCBs are generally much higher (0.3 $\mu g/m^3$) than levels measured in outdoor air (0.004 $\mu g/m^3$).[58] PCB concentrations were measured in the indoor air of several public buildings in Bloomington, IN.[59] The concentrations were 5 to 300 times higher than outdoor concentrations, and the indoor-air PCB levels were highest in buildings having the earliest construction dates. Indoor air ventilation systems were found to be a short-range source, governed by factors such as the building ventilation rate, and it was hypothesized that this building release even constituted a principal source of tri- and tetrachlorinated PCBs at a Birmingham sampling site.[60] Much of the explanation for higher levels in indoor air appears to be linked to the extensive use of fluorescent light ballasts in the past, especially in schools, office buildings, and institutional building, such as hospitals. Each of these ballasts contains approximately 1.6 kg of PCBs. Many of these ballasts can still be found in use even today.[61]

18.2.2 Aquatic and Terrestrial Fate of PCBs

18.2.2.1 Bioaccumulation Pathways of PCBs

PCBs are noted for their tendency to bioaccumulate in aquatic and terrestrial organisms. This characteristic can be depicted by characterizing processes involved in the pharmokinetics of exposed experimental animals.[62] Matthews and Dedrick[62] reviewed this subject and reported their findings for one study in which specific congeners were applied to rats, and the exact chemistry of the compounds and their distribution were carefully followed (Table 18.2). Other rodent studies have shown similar trends for intrabody distribution of PCBs. Notice in Table 18.2 that the more

Table 18.2 Tissue/Blood Distribution Ratios of PCB Congeners in Rats

	Parent				Metabolite			
Compartment	1-CB	2-CB	5-CB	6-CB	1-CB	2-CB	5-CB	6-CB
Blood	1	1	1	1	1	1	1	1
Gut lumen	1	1	1	1	1	1	1	1
Muscle	1	2	1	4	0.14	0.4	0.1	0.3
Liver	1	3	6	12	2	5	2	4
Skin	10	10	7	30	0.25	0.3	0.1	2
Adipose	30	70	70	400	0.4	0.6	0.4	2

	Kinetic Parameters			
Rate constant	1-CB	2-CB	5-CB	6-CB
Metabolic clearance (K_m,mL/min)	10.0	2.0	0.39	0.045
Kidney clearance (K_k,mL/min)	0.2	0.133	0.033	0.03
Biliary clearance (K_B,mL/min)	0.2	0.35	0.3	0.3
Gut reabsorption (K_G,mL/min^{-1})	0.00016	0.00016	0.00016	0.00016
Fecal transport ($K_F$min^{-1})	0.0008	0.0008	0.008	0.0008

Source: Matthews, H.B. and Dedrick, R.L., *Annu. Rev. Pharmacol. Toxicol.*, 24, 85, 1984. With permission.

lipophilic 5/6-chlorobiphenyls tend to preferentially bioconcentrate in fatty tissues (adipose tissue and skin), whereas the more polar members, especially the polar metabolites, tend to show up in the hydrophilic cell tissues/compartments. Note also that the size of the clearance rate constant (Km) is structure-dependent; e.g., the Km for CB-1 is 10, while the values decrease as the chlorine content increases.

In addition to the gross structural character of the molecule that is established by chlorine content, position of the chlorines on the ring also affects distribution and persistence within organisms. For example among the four hexachlorobiphenyls 2,2',3,3',5,5'-; 2,2',3,3',6,6'-; 2,2',4,4',5,5'-; and 2,2',4,4',6,6', the 2,2',3,3',6,6' was eliminated and metabolized more rapidly than were the other three. This was due to the fact that the 4,5 unsubstituted carbons of this congener were not present in the others. In another set of tests, a group of 6-CBs with no *ortho* and only one *ortho* (2 position) was administered. Levels tested after 29 days showed that there were marked differences in retention of these compounds depending on the animal species (fat levels were higher in the mammalian species than in trout and quail): 8.27, 6.84, and 4.74 in the rat, rabbit, and guinea pig, respectively, vs. 3.02 and 2.15, respectively, in trout and Japanese quail. Furthermore, structure also contributed to variations in retention. The quail retained only the non*ortho* congeners; this was true even when low levels were tested. Rabbits retained the highest levels of the di-*ortho* and mono-*ortho* compounds. Fish retained fairly even amounts of all the components and at lower levels of all of the congeners than for the other organisms.

18.2.2.1.1 Aquatic Bioaccumulative Processes of PCBs

The aquatic bioaccumulative fate of PCBs has been studied in several ecosystem types and over numerous food-chain pathways. Several examples to support bioaccumulation can be cited. All of these, however, suffer from lack of control of all of the input parameters and also control as the tiers increase. A dramatic example was described by Safe[63] for the Lake Ontario ecosystem. The chain was depicted to start with water at 0.05 ng/g PCB, then progressing through sediment (150 ng/g) to plankton (1880 ng/g) to catfish at 11,580 ng/g to finally the herring gull at 3,530,000 ng/g. Laboratory studies can overcome the lack of input accountability in environmental examples; however, transferring these findings to the field situation is difficult. Eisler[64] provided a relevant review of information on how the sublethal effects of PCBs on aquatic organisms are linked to their high bioaccumulation potential. Briefly, he demonstrated that the high potential for bioaccumulation of PCBs by aquatic organisms is due to their intimate exposure to these compounds and to the highly lipophilic nature of PCBs, causing them to accumulate in the fatty tissues of these organisms.

Bioconcentration factors are used to express this bioaccumulation tendency. Gobas[65] provides an excellent treatise on distinguishing bioaccumulation factors (BAFs) from bioconcentration factors (BCFs) for PCBs based on 1984 data that he and his co-workers generated for individual PCB congeners.[66] The typical values increase by a factor of 10- to 100-fold when ascending major consumption levels in a food chain, i.e., from algae to fish to birds. Depuration of accumulated PCBs is slow. In fish, egg maturation and spawning can, however, result in significant reduction in the body burden of persistent PCBs such as 2,5,2',5'-tetrachloro-biphenyl.[67]

It is largely the bioaccumulative property of PCBs that has caused them to be identified as ubiquitous contaminants. The chemicals tend to concentrate in fatty organisms that often reside at the peak of food chains. Such food chains are especially common in arctic climates, where fats are the most efficient and common means of energy storage. PCBs are found in nearly all marine plant and animal species, fish, mammals, birds (especially fish-eating birds), and, of course humans. Wassermann and co-workers[68] published an extensive review of PCBs in animals that, with the exception of the highest values, is still generally valid today. Specifically, they reported that for marine food webs, zooplankton range from < 0.003 μg/g to 1 μg/g, whereas top consumers, such as seals and fish, had ranges of PCB from 0.03 to 212 μg/g. Moessner and Ballschmiter[69] monitored

seven indicator congeners of the polychlorinated biphenyls (PCB # 28, 52, 101, 118, 138, 153, and 180) in marine mammals that differed in their geographic distributions. They found that animals from the western North Atlantic were contaminated at levels that were about 15 times higher than for animals from the eastern North Pacific and the Bering Sea/Arctic Ocean.

18.2.2.1.2 Terrestrial Biaccumulative Processes of PCBs

The terrestrial biaccumulative fate of PCBs is less studied, largely because levels tend to be lower and concern for exposure is less than for aquatic organisms. The lower accumulation in terrestrial organisms is believed to be a function of food chains that are shorter than those in aquatic environments.[54] Levels in terrestrial biota can reach high levels in organisms near PCB landfill sites[70] or in terrestrial communities neighboring regions of high aqueous buildup. For example, for eagles were studied in the Great Lakes region; those nearest the lakes had notably higher levels than those farther inland.[71] Also, tree swallows living near the shores of the Hudson River had higher PCB levels than those from river sites more distant from known PCB pollution.[72]

The most extensive and detailed studies of terrestrial transfer of PCBs exist for the Arctic[73] (several studies were summarized in the AMAP, Assessment Report, Arctic Pollution Issues[54]). Extensive study of caribou and reindeer revealed that, even though concentrations of the PCBs were substantially lower in tissues of these terrestrial herbivores than in marine mammals collected from nearby areas, the importance of these herbivores to the native diets in the Arctic makes this route for human exposure one for concern.[54] Levels of PCBs were higher (~twofold) in Russian reindeer (20 ng/g wet weight) than in Canadian caribou. Elkin and co-workers[74] provided an example of a food-chain transfer by way of caribou in the Northwest Territory of Canada; the transfer was from lichens to caribou to wolves. The pattern of congeners changed as the mixture of PCBs was transferred. The food-chain buildup is obvious, with levels reaching a maximum of about 50 ng/g lipid weight in the wolf, after starting around 0.4 ng/g dry weight for the lichens. The congener shift observed with caribou was similar to that observed by Muir and co-workers[75] in marine organisms — fish to seal to polar bear.

Accumulation of PCBs by dairy cows has been studied by several investigators.[76–79] Thomas and co-workers[78] described the distribution fate of PCBs in cows with a concern for terrestrial exposure through forage and consumption. They developed a model that incorporates degradation, especially for the readily metabolized congeners (e.g., BZ#33). Calamari and co-workers[80] studied plant uptake of PCBs and used this as a measure of the geographic distribution of PCBs. Hermanson and Hites[81] looked at uptake by bark as a means of describing geographic distribution of PCBs and other hydrophobic pollutants.

18.2.2.2 Abiotic Dispersal of PCBs

The fate and dispersion of PCBs is greatly influenced by abiotic dispersion processes, volatility, solubility, particle sorption, etc. and these are all important and interactive processes ongoing in the atmospheric and aquatic systems that are the major reservoirs for the world's inventory of PCBs. The concept of inventories is important for an understanding of where likely exposure will occur. One such inventory was conducted by the National Academy of Science in the early 1980s.[21] The accessible PCBs were defined as residing in the mobile environmental reservoir (MER). A major objective of these early assessments was to attempt to balance what was produced with where it had come to rest and to determine how much was still available to contaminate the environment. Much of the existing PCBs at that time (1977) were still in commerce, in storage awaiting destruction, or in reservoirs that were considered inaccessible (landfills, deep sediment, or degraded). Tanabe,[82] using updated information (1987 data), performed a similar exercise and calculated the global distribution of available PCB. Despite the passage of 10 years between the two estimates, there was remarkable similarity between them (Figure 18.3). Tanabe further indi-

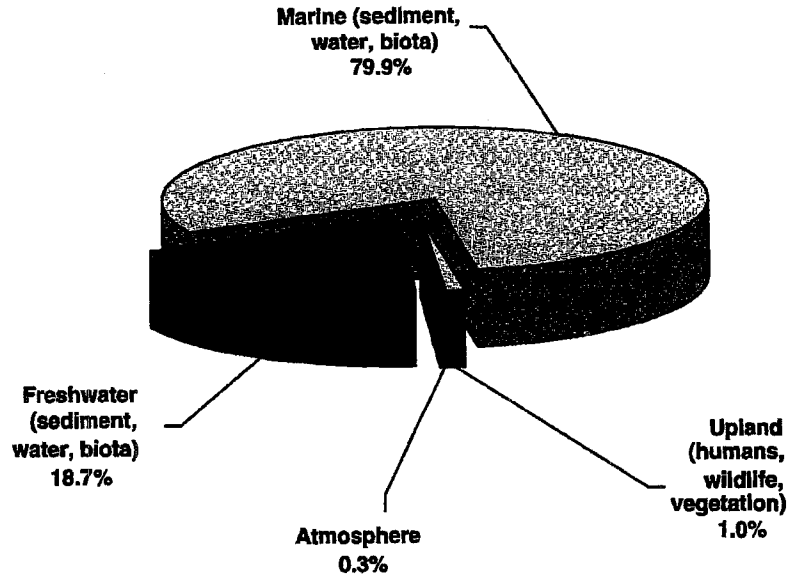

Figure 18.3 Global distribution of environmentally available PCB, as estimated by Tanabe.[82]

cated the need for increased concern for the marine mammals that would be receiving the greatest exposure according to these predictions. Most recent inventories for PCBs have been developed for specific regions of the country. Harrad and co-workers[57] describe the present United Kingdom environmental levels of PCBs. Only 1% of the amount of PCBs sold in the United Kingdom since 1954 was found to still be present in the U.K. environment. Across the range of congeners, persistence increased with increasing chlorination. The major loss mechanism for PCBs was advection, atmospheric or pelagic, transport from the United Kingdom. There was a dramatic fall in levels in archived soils and vegetation between the mid-1960s and the present. Ninety-three percent of the contemporary U.K. burden is associated with soils, with 3.5% in seawater and 2.1% in marine sediment. Freshwater sediments, vegetation, humans, and sewage sludge combined to account for only 1.4% of the present burden, and PCB loadings in air and freshwater were insignificant. The major loss pathway from the United Kingdom is atmospheric, with sources feeding this atmospheric advection as follows: volatilization from soils (88.1%), leaks from large capacitors (8.5%), production of refuse-derived fuel (RDF) (2.2%), leaks from transformers (0.6%), recovery of contaminated scrap metal (0.5%), and volatilization from sewage sludge-amended land (0.2%).[57]

18.2.2.2.1 Atmospheric Dispersal of PCBs

The air concentrations of PCBs and other chemicals play an important role in the deposition of these chemicals in terrestrial ecosystems (on leaves/needles, grass, soil).[57,83] Long-range overland transport of PCBs is critically linked to atmospheric routes of exposure; this mechanism was clearly demonstrated for transport of PCBs in Canadian lakes by Muir and co-workers.[84] The conclusion from this study was that atmospheric movement northward, and subsequent fractionation by volatility, led to selective changes in the PCB profile in the liver of burbot that inhabited these lakes. The PCB profiles progressed from a preponderance of heavier (less volatile) to lighter (more volatile) PCB homologs in the burbot livers in lakes dispersed with increasing latitudes north.

The importance of atmospheric processes for dispersal of PCBs has been established on a global scale.[56,85,80] Higher levels occur downwind of known sources, e.g., the Chicago plume[86] and landfill

sources.[87] Considerable data, especially on the Great Lakes, have been recorded to indicate that PCBs will exchange across the air/water interface[88,89] and that this process is controlled by temperature, mass balance levels in the air and water, and wind speed.[90] Actually, realization of this process has helped greatly towards reconciling the amount of PCB that could be accounted for by measurements in sediment and water column of the Great Lakes with the predicted amounts based on loadings. Realization of a reverse flux, i.e., gaseous losses out of the water column, has allowed researchers to account for the imbalance in their previous estimates and provided a means for mass balance estimates that include dynamic exchange of PCBs as gases across the air/water interface.

The best predictive chemical constant for describing these fluxes is the compounds' Henry's Law constant (air–water partition coefficient); H-values have been calculated for a considerable number of PCB congeners. Typical values for the estimated Henry's Law constants for Aroclors indicate that water-to-air degassing can be a significant environmental transport process for PCBs when they are in disequilibrium in water vs. overlying air, especially when water temperatures are high and air concentrations are low, e.g., during autumn over the Great Lakes.[90] Reported H-values for the Aroclor mixtures 1242 and 1260, respectively, were 58.5 and 731 Pa m^3/mol.[91] Burkhard and co-workers[92] developed a method by which to estimate H-values for the congeners; their estimated values compared favorably with the limited measured values that were available previously. A recent review of H-values for all 209 of the PCB congeners[93] indicates that there is wide range in values (varying from 160 Pa m3/mol for BZ#9, a dichlorobiphenyl, to 1.00 Pa m3/mol for BZ#199, which is an octochlorobiphenyl). Bamford and co-workers[94] recently generated measured H-values for 26 congeners, including direct measurements for their changing values as functions of temperature (–3 to 31°C). This is an important property to consider, especially for environmental modeling.

Wania and Mackay[55] described the relative mobility of PCB homologs on a global scale by using vapor pressure and log octanol–air partition coefficients of PCBs. They grouped PCBs into four categories based on the relative mobilities of the PCBs to move away from sources and toward the poles. These groupings were: 0 to 1 Cl (highly mobile worldwide/no deposition), 1 to 4 Cl (relatively high mobility/deposition in polar latitudes), 4 to 8 Cl (relatively low mobility/deposition in mid-latitudes), and 8 to 9 Cl (low mobility/deposition close to source).

Model predictions of the concentration of PCBs in air can be made by knowing the slope of the log vapor pressure vs. inverse temperature curve (Antoine equation) as well as the expected air concentrations of particulate matter.[95] It has been shown by other researchers that atmospheric PCB concentrations, which are only weakly dependent on transport paths, are strongly dependent on temperature because of the vapor pressures of the compound.[96]

The major source of PCBs to vegetation is transfer of vapor-phase PCBs from air to the aerial aboveground portions of the plants.[97] Harner and co-workers[98] measured atmospheric PCBs near hazardous waste sites that were greater than background. Their conclusion was that PCBs were being emitted from the soils near these sites where previous deposition had occurred. Also, losses from moist soil are greater than from dry soil, due to stronger soil binding in the absence of water.[99]

18.2.2.2.2 Aquatic Dispersal of PCBs

Abiotic-mediated movement and fate of PCBs in aquatic systems has been monitored extensively and in every conceivable situation: open ocean,[100,101] rivers (see numerous references cited throughout text), large lakes (Lake Baikal,[56,102,51] Great Lakes[48]), small arctic lakes,[103] and embayments and estuaries.[41,104,44]

In water, adsorption to sediment or other organic matter is a major PCB removal process. Experimental and monitoring data have shown that PCB concentrations are higher in sediment and suspended matter than in the associated water column. The low water solubility and, therefore, resulting high octanol–water partition coefficients (expressed by the log K_{ow}) range from 4.5 to 8.1 for individual PCB congeners[105] and result in a strong adsorption to soils and sediments, suggesting that leaching should not occur in soil under most conditions. If leaching does occur, it will be

Table 18.3 Ranges of Physicochemical Properties of Polychlorobiphenyls ($C_{12}H_{10-n}Cl_n$)

Homolog Group	Molecular Weight (μg/L)	Solubility (Pa) 20°	Vapor Pressure	Log K_{ow}
Monochloro-	188.7	1.3×10^3–7×10^3	2.2×10^3–9.2×10^2	4.6–4.7
Dichloro-	223.1	0.6×10^2–7.9×10^2	3.7×10^2–7.5×10	5.2–5.3
Trichloro-	257.6	0.1×10^2–6.4×10^2	1.1×10^2–1.3×10	5.7–6.1
Tetrachloro-	292.0	0.2×10^2–1.7×10^2	1.8–4	5.9–6.7
Pentachloro-	326.4	4.5–12	5.3–0.88	6.4–7.5
Hexachloro-	360.9	0.4–0.9	1.9–0.2	6.4–7.6
Heptachloro-	395.3	0.5	0.53–4.8×10^{-2}	7.0–7.7
Octachloro-	429.8	0.2–0.3	7.8×10^{-2}–9×10^{-3}	7.0–7.6
Nonachloro-	464.2	0.1	3.2×10^{-2}–1.1×10^{-2}	7.7–7.9
Decachloro-	498.7	0.02	5.6×10^{-3}	8.4

Source: Ballschmiter, K. et al., in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*, Kimbrough, R.D. and Jensen, A.A., Eds., Elsevier, Amsterdam, 1989. With permission.

greatest for the least-chlorinated congeners. These trends in physical properties are apparent in Table 18.3.

Although adsorption and subsequent sedimentation may immobilize PCBs for relatively long periods of time in aquatic systems, redissolution into the water column has been shown to occur. The substantial quantities of PCBs contained in aquatic sediments can therefore act as a reservoir from which PCBs may be released over long periods of time. Since sorption to soil is proportional to the soil's organic carbon content,[107,108] leaching or loss is expected to be greatest from soils with low organic carbon.

An interesting discovery in remote pristine lakes in the arctic was the differentiation of atmospheric loading from biotransported PCBs. Grayling were monitored to measure background levels in the water. One grayling population was in a salmon-spawning lake, and the other in a nearby lake without salmon and receiving pollutants only via atmospheric deposition. The grayling in the salmon-spawning lake had concentrations of PCBs more than twofold higher than those in the grayling in the salmon-free lake, and the pollutant composition resembled that found in salmon.[103]

18.2.3 PCB Removal Processes

Significant removal of PCBs from the MER can occur through natural processes. One process in the aquatic system is simple physical removal due to sediment burial. However, permanent removal by degradation is the preferred method for ultimate protection of the environment. Chemical degradation in natural systems is minimal,[109] except for photolysis. Anderson and Hites[110] measured hydroxyl radical degradation as it occurs during photolytic exposure. They estimated half-lives ranging from 2 to 34 days for several PCB congeners. Atkinson[111] reviewed the literature on the atmospheric chemistry of PCBs and verified that losses due to photolysis can be high. Tropospheric half-lives due to hydroxyl radical removal were listed as follows: mono-, 3.5 to 7.6 days; di-, 5.5 to 11.8 days; tri-, 9.7 to 20.8 days; tetra-, 17.3 to 41.6 days; and penta-, 41.6 to 83.2 days.

Biological degradation is slow, according to most studies performed over a wide range of organisms including higher animals, plants, and several microbial systems. PCBs are very resistant to biological transformation — one of the very features of the group that made them useful in commerce. In spite of the abundant evidence for PCBs' ability to resist biological degradation, much study has gone into attempting to isolate a "bug" or consortium of bugs that will magically clean up the numerous hot spots of PCB known to exist in the environment.[112, 113]

18.2.3.1 Biological Degradation of PCBs

Metabolism of PCBs by biological systems has been studied extensively. Several reviews of this subject are available.[62,114–116] Invariably, the phenolic products are the major PCB metabolites,

although sulfur-containing metabolites (sulfones), *trans* dihydrols, polyhydroxylated PCBs, and their methyl–ether derivatives and ring-degraded microbial oxidation products have been identified. The effects of chlorine substitution patterns on oxidative breakdown seem to fall into the following patterns:[114]

1. Hydroxylation is favored at the *para* position in the least-chlorinated phenyl ring, unless this site is sterically hindered.
2. In the less-chlorinated biphenyls, the *para* position of both biphenyl rings and the carbon that is *para* to the chlorine are all readily hydroxylated.
3. The availability of two vicinal unsubstituted carbon atoms (particularly C-5 and C-4 in the biphenyl nucleus) also facilitates oxidative metabolism of the PCB substrate, but it is not a necessary requirement for metabolism.
4. As the degree of chlorination increases on both phenyl rings, the rate of oxidative metabolism decreases.
5. The metabolism of specific PCB isomers by different species can result in considerable variations in metabolite distribution. Most PCB congeners, particularly those lacking adjacent unsubstituted positions on the biphenyl rings (2,4,5-, 2,3,5-, or 2,3,6- substituted on both rings), are extremely persistent in the environment.

Harner and co-workers[98] have suggested that microbial degradation half-lives on the order of 10 years are possible; however, the actual values are likely congener-specific and are also a function of concentration and microbial condition in the soil. Biodegradation of PCBs in sediment can occur under both aerobic[117] and anaerobic[118] conditions. Biodegradation rates are highly variable because they depend on a number of factors, including the amount of chlorination, concentration, type of microbial population, available nutrients, and temperature. Results show, however, that under aerobic conditions, mono-, di-, and trichlorinated biphenyls generally biodegrade relatively fast; tetrachlorinated biphenyls generally biodegrade slowly; and the more highly chlorinated biphenyls generally resist biodegradation.

Studies of subsurface anaerobic biodegradation of aquatic sediment show that the pattern of congener reactivity is determined by two main factors — reductive potential of the system and molecular shape of the PCBs. PCBs containing chlorines in the *para* positions are preferentially biodegraded, compared to PCBs containing chlorines in other ring positions,[119] and meta chlorines appear to be preferentially lost. Studies from spill sites also show that the highly chlorinated congeners are biotransformed by a reductive dechlorination to less-chlorinated PCBs, which are biodegradable by aerobic processes.[120,121] For highly chlorinated PCBs that have been shown to dechlorinate naturally in anaerobic sediments, there appears to be a concentration threshold (10 µg/g dry weight) below which this anaerobic process will not start.[118,119]

Biodegradation is probably the ultimate loss process for PCBs in sediments (at least in surficial zones); however, diagenesis experiments in deeper sediments need to be carried out in order to assess the lifetime of PCBs that are deeply buried. Biodegradation in soils with high organic carbon content is slower than in less organic-carbon-enriched soils.[122]

18.3 SOURCES AND PATHWAYS OF PCDDs AND PCDFs IN THE ENVIRONMENT

18.3.1 Release of PCDDs and PCDFs into the Environment

18.3.1.1 Emission of PCDDs and PCDFs into Water

PCDDs and PCDFs are formed as by-products in several chemical manufacturing processes. In the case of PCBs, a PCDF molecule can be formed by ring closure of a PCB molecule in the

presence of oxygen. While industrialized countries ceased producing PCBs in the 1970s, PCDF concentrations in commercial PCB formulations used prior to that time were reported to range from less than 1 mg/kg to more than 10 mg/kg.[123–125] PCBs were used primarily as dielectric fluids in transformers and capacitors (see section on PCBs above), and additional formation of PCDFs has been found to occur in catastrophic events such as arcs and electrical fires, with concentrations of total PCDFs as high as 2000 mg/kg on soot particles from PCB fires.[126] Certain dielectric fluids also contain chlorobenzenes (CBs) in addition to PCBs. While the CBs can also be converted to PCDDs by catastrophic events, the reaction is bimolecular, and therefore the PCDD concentrations are two orders of magnitude lower than the PCDF concentrations.

Emissions into the aquatic environment from PCB fires can be controlled, and any contamination is usually confined to a small area. In contrast, operations associated with the manufacturing and servicing of electrical equipment or with the improper disposal of capacitors and transformers have resulted in more widespread contamination of the aquatic environment by both PCDFs and PCBs.

Chlorophenols (CPs) are contaminated with PCDDs/PCDFs, and the manufacture and utilization of these compounds have resulted in the release of PCDDs/PCDFs into the aquatic environment. Pentachlorophenol (PCP) has been widely used as a fungicide and insecticide in the wood-products industry, and 2,4,5-trichlorophenol (TCP) was used as the precursor of the herbicide 2,4,5-T. At one time, 2,4,5-T was used extensively in the United States and other industrialized countries as a herbicide on grasslands where cattle and sheep were grazed, on rice-growing fields, in the control of deciduous species in conifer forests, and along roadsides. The toxic 2,3,7,8-TCDD is the major PCDD/PCDF contaminant in 2,4,5-T, and concentrations exceeding 10 mg/kg were found in certain 2,4,5-T formulations produced between 1966 and 1970.[127] However, these were unusually high concentrations, since most 2,4,5-T formulations produced in the 1960s did not contain 2,3,7,8-TCDD concentrations greater than 0.2 mg/kg.[128,129]

The production of PCP in the United States was 20 million kg in 1976 and 14.5 million kg in Japan in 1966.[130] After 1971, production ceased in Japan, but the compound is still produced at one plant in the United States. There are no production figures available for Europe. Results from a number of studies have shown that mg/kg concentrations of hexa-, hepta- and octa-CDDs and CDFs are present in commercial formulations of PCP, with reported concentrations varying over several orders of magnitude.[131] One manufacturer produced a purified PCP formulation that contained less than 25 mg/kg of total PCDD/PCDF compounds.[132] The toxic properties of the PCDD/PCDF compounds in PCP can be attributed to the presence of 1,2,3,6,7,8-hexa CDD. This isomer accounts for nearly 50% of the total hexa CDD concentration in some PCP formulations.[132]

The PCDD/PCDF compounds associated with CPs can be released into water either during manufacturing operations or during the use of the products. Sediments in the vicinity of many chlorophenol-manufacturing plants in the United States and Europe have become contaminated with PCDD/PCDF compounds. A plant situated on the Passaic River 3 km upstream from Newark Bay produced approximately 15 million tons of 2,4,5-T between 1948 and 1969. Sediment samples collected from different locations were dated by radiochemical methods and were analyzed for tetra-, hepta- and octa-CDDs and CDFs.[14] Immediately outside the plant a sediment core section from the mid-1960s was contaminated with 7600 pg/g of 2,3,7,8-TCDD, whereas a 1985 section from the same core had a 2,3,7,8-TCDD concentration of 730 pg/g (all sediment concentrations of PCDDs/PCDFs reported in this subsection are expressed on a dry-weight basis). Samples taken further downstream in Newark Bay and in New York Harbor had considerably lower concentrations of 2,3,7,8-TCDD but were contaminated with PCDDs/PCDFs whose patterns were statistically associated with other sources of contamination.[134]

While the utilization of 2,4,5-T has undoubtedly contributed to 2,3,7,8-TCDD contamination in the aquatic environment, it is generally not possible to determine the point sources for this contamination. However, it is possible to determine aquatic contamination by PCDD/PCDF compounds from facilities where wood is treated with PCP. In a wood treatment plant in Pensacola, Florida, that was closed in 1981, it was found in 1984 that sludge and sediments from wastewater

impoundments were contaminated with total hexa- to octa-CDD concentrations of 49 and 105 mg/kg, respectively.[135] It was found by taking soil samples at 0.3 and 0.6 m depths that subsurface migration had occurred, with total PCDD concentrations decreasing from 1.1 mg/kg near the impoundment site to 9.9 ng/g at a distance of 275 m from the site. Sediments collected in the harbor of Thunder Bay, Ontario, near a wood-treatment plant also showed evidence of PCDD/PCDF contamination, with a maximum level of 1.3 ng/g.[136]

In 1985, during the course of the U.S. EPA National Dioxin Study, a comprehensive study on PCDD/PCDF contamination in the United States, it was discovered that fish collected downstream from pulp and paper mills that used the kraft process were contaminated with 2,3,7,8-TCDD.[137]

Subsequent investigations showed that the PCDD/PCDF compounds were primarily formed during the chlorination stage of the pulp-bleaching process.[138,139] Only a small number of isomers were formed, with 2,3,7,8-TCDF as the dominant isomer, followed by either 2,3,7,8-TCDD or octa CDD.[140,141] These results are consistent with a mechanism of direct chlorination of dibenzo-*p*-dioxin (DD) and dibenzofuran (DF). It was shown that both DD and DF were present at ng/g levels in petroleum-based defoaming agents formerly used in pulp processing.[142] However, the PCDD/PCDF compounds must also have been formed by other reaction mechanisms, since lignin from which all low-molecular-weight compounds had been removed by methanol extraction formed the PCDD/PCDF compounds in the presence of chlorine.[139] Based on a study of 104 pulp and paper mills in the United States, it was found that the average export of 2,3,7,8-TCDD from a mill site was uniformly distributed in three media: pulp 38%, effluent 29%, and sludge 33%.[143] For the kraft mills involved in the study, mean concentrations of 2,3,7,8-TCDF in softwood pulp, effluent, and sludge were 137, 0.5, and 806 pg/g, respectively, and mean concentrations of 2,3,7,8-TCDD in the same media were 12, 0.06, and 95 pg/g, respectively. Comparable concentrations of the two analytes were found in the effluents of Canadian pulp and paper mills.[141] In the 1990s, defoaming agents containing PCDD/PCDF precursors were eliminated, and steps were taken to replace chlorine as a bleaching agent by other products, primarily chlorine dioxide. Studies conducted in Canada have shown that these process changes have resulted in > 90% reduction in the levels of 2,3,7,8-TCDF and 2,3,7,8-TCDD discharged to the environment from pulp and paper mills.[144–146]

The sludges from pulp and paper mills are frequently used for the fertilization of agricultural lands and therefore can serve as a source of PCDD/PCDF contamination for both terrestrial and aquatic environments. Sludge from sewage treatment plants is frequently used for the same purpose, and results from several investigations have shown that the sewage sludges from industrialized countries are contaminated with PCDD/PCDF compounds, primarily hepta-CDDs and octa-CDD.[147,148] There has been a trend toward decreasing concentrations over time, with current mean PCDD/PCDF concentration in sewage sludges from Catalonia, Spain of 55 pg I-TEQ/g (International Toxic Equivalents[149]), compared to 620 pg I-TEQ/g in the period from 1979 to 1987.[147] For a full discussion of TEQ (dioxin-like toxicity, toxicity equivalency factors and toxicity equivalents), see Section 18.6, Effects of PCBs, PCDDs, and PCDFs.

A predominant source of the PCDD/PCDF compounds in sewage sludge has not been identified. However, there is evidence from the United Kingdom to suggest that combustion and PCP may be major sources of PCDDs/PCDFs in sewage sludges.[148] Furthermore, a study conducted in Germany showed that household wastewater from the washing of PCP-treated textiles contributed between 27 and 94% of the PCDDs/PCDFs in sewage sludge from a nonindustrial area.[147] Additional sources of PCDDs/PCDFs in sewage sludge are textile dyes and formation from precursors during sludge digestion.

Precursor compounds with structures closely related to PCDD/PCDF compounds are present in the chemical processes described above. However, virtually every chemical process in which there is a source of carbon and chlorine has the potential to produce PCDD/PCDF compounds, with the concentrations decreasing as the structures of the precursor compounds deviate from PCDD/PCDF structures. It was found in 1974 that commercial preparations of hexachlorobenzene were contaminated with octa-CDF (0.4–58 mg/kg) and octa-CDD (0.05–212 mg/kg).[150] Only traces

(pg/g) of PCDD/PCDF compounds were found in commercial preparations of short-chain chlorinated hydrocarbons.[151] However, these compounds have low boiling points, and high PCDD/PCDF concentrations were found in sediments near waste-discharge points from a vinyl chloride monomer plant in Finland.[152]

18.3.1.2 Emissions of PCDDs and PCDFs into the Atmosphere

It was originally considered that PCDD/PCDF compounds were only formed as by-products in the manufacture of chlorinated aromatic chemicals. However, in 1977, PCDD/PCDF compounds were found in the flue gases from several municipal incinerators in the Netherlands.[153] A study carried out in 1978 showed that PCDD/PCDF compounds were present in cigarette smoke and in particulate matter from chemical and municipal waste incinerators, automobile and diesel truck mufflers, charcoal-broiled steaks, and fireplaces.[154] Based on these results, it was concluded that PCDD/PCDF compounds were ubiquitous by-products of combustion processes.

Municipal waste incinerators (MWIs) are generally considered to be a major combustion source of PCDD/PCDF compounds, and there are numerous reports in the literature on the determination of PCDDs/PCDFs in both ash by-products (fly-ash and bottom ash) and stack gas emissions. There is considerable variability in the patterns of PCDD/PCDF compounds found in MWI samples, but in general the PCDDs are dominated by octa-CDD, with concentrations of the other congener groups decreasing as the number of chlorine atoms is reduced. In contrast, the PCDFs, which are generally present at higher concentrations than the PCDDs, are dominated by less-highly-chlorinated congeners — usually either penta- or hexa-CDF congeners.[155] The absolute amounts of PCDD/PCDF compounds in stack gas emissions from 32 MWIs in industrialized countries varied from < 1 to 33,047 ng/dry standard cubic meter (ng/DSCM).[156] Data compiled by the WHO Regional Office for Europe also showed that there were large differences in the concentrations of 2,3,7,8-substituted PCDD/PCDF compounds emitted by different municipal MWIs.[157,158] The higher concentrations were often associated with abnormal operating conditions during the sampling program. Older incinerators and incinerators with inadequate emission-control equipment also had higher PCDD/PCDF emissions. The stack gas emissions of most MWIs in industrial countries are now close to the desired limit (0.1 ng I-TEQ/m^3).[159]

In comparison to MWIs, hazardous waste incinerators (HWIs) consume a much smaller quantity of waste. However, the concentrations and the patterns of PCDD/PCDF compounds emitted by state-of-the-art HWIs are similar to those found for municipal incinerators, although the waste stream in the former often contains large quantities of chlorinated chemicals.[158] While hospital incinerators also consume a relatively small quantity of waste, emissions of PCDD/PCDF compounds from these incinerators can be high.[160,161] In Denmark, it was estimated that 1,750,000 and 16,800 tons of waste were burned annually in MWIs and in hospital incinerators, respectively.[162] However, the total amounts of PCDD/PCDF compounds produced were 2200 g and 900 g, respectively. The high concentrations of PCDD/PCDF compounds in hospital incinerator emissions have been attributed to the presence of a high percentage of plastics in hospital wastes.[163] Also, these incinerators were often poorly designed, and it is now agreed that incinerators of advanced design should be used for the destruction of hospital waste.

Metal-processing plants are also a source of atmospheric PCDD/PCDF compounds. In Sweden in 1992, it was reported that steel mills were the single largest source of PCDD/PCDF compounds.[164] In the case of scrap-metal-reclamation plants, the presence of chlorine-containing plastics, such as polyvinyl chloride (PVC), in the feedstock would appear to be one of the factors responsible for the increased PCDD/PCDF production.[165] However, other factors, such as furnace design, also are important in controlling PCDD/PCDF emissions.[166]

Studies conducted in Sweden[167] and New Zealand[168] showed that automobiles represented an additional source of PCDD/PCDF compounds in the atmosphere when leaded gasoline was used as a fuel, with TCDFs as the major congener group in the emissions. However, no PCDDs/PCDFs

were identified in emissions from automobiles using unleaded gasoline, suggesting that the lead scavenger dichloroethane was the source of the PCDDs/PCDFs. While diesel-powered vehicles are still a source of PCDD/PCDF emissions, data from stationary engine tests[169] in Europe and from on-road sampling[170] in the U.S. suggest that these emissions contribute less than 10% of the total atmospheric emissions of PCDDs/PCDFs.

As PCDD/PCDF emissions from incinerators are being reduced by the introduction of new technology, diffuse burning sources, including domestic heating, are making a larger contribution to the total load of atmospheric PCDDs/PCDFs. Based on tests conducted at the U.S. EPA's Open Burning Test facility, it was estimated that between 2 and 40 households burning their trash daily in barrels could produce PCDD/PCDF emissions comparable to a 182,000 kg/day MWI.[171] Bonfires are customarily lit in the United Kingdom during a November festival, and it was determined that PCDD/PCDF emissions during the festival amounted to ~5 to 14% of the United Kingdom's total annual emissions from primary sources.[172]

18.3.2 Aquatic and Terrestrial Fate of PCDDs and PCDFs

18.3.2.1 Bioaccumulation Pathways of PCDDs and PCDFs

18.3.2.1.1 Aquatic Bioaccumulation Pathways of PCDDs and PCDFs

There are three potential reservoirs of PCDDs/PCDFs available to aquatic organisms: water, sediment (suspended and bottom), and food. The importance of each reservoir as a source of PCDDs/PCDFs for fish was studied in a laboratory investigation of 2,3,7,8-TCDD bioaccumulation in Lake Ontario. It was found, using various combinations of contaminated food, sediment, and water, that food was the major source of 2,3,7,8-TCDD for lake trout (*Salvelinus namaycush*).[173] Only 22 to 30% of the 2,3,7,8-TCDD residue in the lake trout was derived from the sediment, and insignificant quantities of 2,3,7,8-TCDD were bioaccumulated from water.

However, the lake trout is a piscivorous species, and results from laboratory experiments conducted with a planktivorous species, guppy (*Poecilia reticulata*), and fly-ash extracts as a PCDD/PCDF source showed that the contribution of food residues to the body burdens of five PCDDs/PCDFs was less than 5% of the contribution from water.[174] A direct comparison with the Lake Ontario study is not possible, since 2,3,7,8-TCDD was not detected in the guppies. An additional bioaccumulation study was carried out with guppies in which one group of fish was exposed to the PCDD/PCDF fly-ash extract dissolved in water and another group was exposed to the same water solution that had been equilibrated with sediment prior to addition to the exposure tanks.[175] While the PCDD/PCDF concentrations in the water were the same in both experimental groups, fish exposed to the sediment-equilibrated water had lower PCDD/PCDF concentrations. It was suggested that PCDD/PCDF compounds in the sediment-equilibrated water were associated with dissolved or colloidal matter and that this association hindered the uptake of the compound across the cell membrane.

For the fish exposed to the sediment-equilibrated water, the bioaccumulation potential for different PCDD/PCDF compounds was evaluated by calculating biota–sediment accumulation factors (BSAFs). The BSAF is defined as the ratio of the concentration of a chemical in tissue lipid to the concentration in sediment organic carbon. This is a very useful parameter since sediment is the major reservoir of PCDDs/PCDFs in the aquatic environment. Also, these hydrophobic compounds associate with organic carbon in sediment and with lipid in biota; therefore, it is possible to compare data from studies in which there are differences in tissue lipid content and organic carbon content. If the affinities of the PCDDs/PCDFs were equal in lipid and in sediment, the BSAFs should approach one and should be independent of a compound's hydrophobicity. However, the BSAFs were all found to be less than one, and they decreased with increasing chlorine content, e.g., from 0.15 for 2,3,7,8-TCDD to 0.003 for OCDD. While the exposures were carried out for

the comparatively short period of 30 days, the results could not be attributed to a failure to reach equilibrium, since comparable BSAFs were found when carp (*Cyprinus carpio*) were exposed for 205 days to contaminated Wisconsin River sediments.[176]

In practice, PCDDs/PCDFs may have different affinities for organic carbon and lipids, and these affinities could be influenced by hydrophobicity. Reductions in water solubility or diffusion across biological membranes are other factors that could explain the decrease in BSAF values as molecular weights increase. Sediments in the marine environment can also be a source of PCDDs/PCDFs for aquatic organisms. Sandworms (*Nereis virens*), clams (*Macoma nasuta*), and grass shrimp (*Palaemontes pugio*) were found to bioaccumulate 2,3,7,8-TCDD, 2,3,7,8-TCDF, and PCBs when exposed to sediments from the Passaic River in New Jersey.[177] While clams rapidly accumulated and depurated the compounds, the highest concentrations were found in the worms, which had slower rates of accumulation and depuration.

In their larval stages, aquatic insects are in intimate contact with sediments; it has been found that the emerging insects can serve as a means of transporting contaminants into aquatic and terrestrial food chains. When small areas of Canadian lakes were isolated as mesocosms by polyethylene barriers, it was determined that up to 2% of a dose of tritiated 2,3,7,8-TCDF in the sediment could be exported annually by emerging insects.[178]

Fly ash from incinerators represents a major atmospheric source of PCDDs/PCDFs (see below), and fly-ash particles are undoubtedly present in many sediment-deposition layers of the Industrial Age. Results from a study on the bioavailability of 2,3,7,8-TCDD from municipal incinerator fly ash to carp suggest that PCDD/PCDF bioavailability from fly ash in the aquatic environment can vary over a wide range, depending on the source of the fly ash and on its organic carbon content.[179] It was found that carp exposed to a fly ash from the East Coast with a high organic carbon content (4%) had lower 2,3,7,8-TCDD residues than did carp exposed to fly ash from the Midwest with a lower organic carbon content (1%), even though the East Coast fly ash had 12 times as much 2,3,7,8-TCDD. In a follow-up study with the Midwest fly ash, BSAF values were determined for selected PCDDs/PCDFs.[180] The BSAFs for tetra- to hepta-CDDs decreased from 7.4×10^{-4} to 7.8×10^{-5}, and for tetra- to hepta-CDFs from 5.7×10^{-4} to 9.2×10^{-5}. These BSAFs are considerably lower than the BSAFs reported for sediments. However, certain fly ashes are highly contaminated with PCDDs/PCDFs and therefore could contribute more strongly to PCDD/PCDF body burdens found in fish.

There are also several field investigations of the food-chain bioaccumulation of PCDDs/PCDFs in aquatic birds. In the first study, PCDD/PCDF concentrations in the livers of Dutch fish-eating birds, primarily of cormorants (*Phalacrocorax carbo*), were compared to PCDD/PCDF concentrations in eels (*Anquilla anquilla*), an important food source for cormorants.[181] The major contaminant in the cormorant liver tissue was 2,3,4,7,8-penta-CDF, followed by 2,3,7,8-TCDD and 1,2,3,7,8-hexa-CDD. These compounds were also found at lower concentrations in the eel tissue. Significant correlations (r values from 0.8 to 0.95, $p < 0.05$) were found between the congener concentrations in the cormorants. It was proposed that this pattern was a result of exposure to a relatively constant mixture of PCDDs/PCDFs via a food source such as the eels. Direct uptake from sediments was considered an unlikely bioaccumulation route since sediment PCDD/PCDF concentrations in the Netherlands are highly variable.

In the second study, concentrations of PCDDs/PCDFs, PCBs, and organochlorine pesticides in the eggs, livers, and whole-body tissues of Lake Ontario herring gulls were compared to the PCDD/PCDF concentrations in alewife (*Alosa pseudoharengus*).[182] The alewife and the rainbow smelt (*Osmerus mordax*) constitute the major fish species in the gulls' diet, and both species contain nearly identical concentrations of organochlorine contaminants. Biomagnification factors (BMFs) are ratios of the PCDD/PCDF concentrations in biota at one trophic level and the PCDD/PCDF concentrations in their food from a lower trophic level.

By using BMFs based on wet-tissue weight rather than lipid weight, we can compare results from the Dutch study with the herring gull study. The BMFs for 2,3,7,8-TCDD, 1,2,3,6,7,8-hexa

CDD, and 2,3,4,7,8-penta CDF in the livers of the cormorants were 12, 29, and 340, respectively, compared to 12, 30, and 9, respectively, in the livers of the Lake Ontario herring gulls. The BMFs for the two PCDDs are in close agreement, whereas there is a large discrepancy in the values for 2,3,4,7,8-penta-CDF. The discrepancy could be due to species differences in liver retention, elimination rates, or unidentified food sources. In the herring gull study, liver concentrations were compared to whole-body concentrations. On a lipid-adjusted basis, the liver/whole-body ratios for the PCDDs/PCDFs exceeded those found for other organochlorine compounds and varied from 1.4 for 2,3,7,8-TCDD to 12 for octa-CDD. It has been found in rats that 2,3,4,7,8-penta CDF binds to nonmetabolizing sites on the protein of the microsomal oxidase cytochrome P-448.[183] This was considered a plausible explanation for the increase in liver retention of the PCDDs/PCDFs in the herring gulls as the degree of chlorination increased.

It is now understood that if the tissue levels of certain PCB congeners that share structural similarities with PCDDs/PCDFs ("dioxin-like" PCBs) are high enough, the TEQ contributions of these congeners may be much more significant than those of the PCDDs/PCDFs. The importance of PCBs in contributing to toxicity can be illustrated by results from a study conducted in the western Mediterranean. In this study, eggs were collected from nests of the Audouin's Gull (*Larus audouinii*), a protected piscivorous species, and the yellow-legged gull (*Larus cachinnans*), a scavenging species that feeds mainly at refuse dumps[184]. The total I-TEQs from PCBs and PCDDs/PCDFs were 2955 and 126 pg/g dry weight in the Audouin's gull eggs and in yellow-legged-gull eggs, respectively. However, the PCDD/PCDF contributions to these total TEQ values were less than 3%. The presence of higher total TEQs in Audouin's gulls can be explained by the higher trophic level occupied by this species relative to yellow-legged gulls.

Aquatic biota are exposed to both 2,3,7,8-substituted- and non-2,3,7,8-substituted PCDDs/PCDFs. However, only 2,3,7,8-substituted PCDD/PCDF isomers are bioaccumulated/biomagnified in vertebrates, although in certain cases non-2,3,7,8-substituted PCDDs/PCDFs can be found in invertebrates. The preferential bioaccumulation of 2,3,7,8-substituted PCDDs/PCDFs in vertebrates has been confirmed by a large number of both field and laboratory studies. Metabolism or selective absorption and retention are possible explanations for this effect.

18.3.2.1.2 Terrestrial Bioaccumulation Pathways of PCDDs and PCDFs

There is a much wider dispersion of PCDD/PCDF compounds in the terrestrial environment than in the aquatic environment, and the potential for terrestrial bioaccumulation is generally considered low. However, industrial accidents have occurred that have resulted in localized contamination by PCDDs/PCDFs. After an explosion at a trichlorophenol manufacturing facility at Seveso near Milan in 1976, severe mortality was found in domestic rabbits raised in areas near the chemical plant. In the group of 341 samples that had positive signals for 2,3,7,8-TCDD, liver concentrations for the analyte ranged from 0.25 ng/g to 1025 ng/g.[185] A fire at a pentachlorophenol wood-treatment facility at Oroville, California, in 1987 contaminated the soil of surrounding farmland with PCDD/PCDF compounds, which were subsequently bioaccumulated by farm animals. There was some suggestion that livestock had been exposed to PCDD/PCDF compounds prior to the fire since a cow slaughtered prior to the fire had the same concentration of PCDD/PCDF compounds as a cow slaughtered after the fire.[186] A controlled laboratory study was carried out in which chickens were fed a formulated diet containing 10% contaminated soil from the area. Approximately 20–50% of the 2,3,7,8-substituted tetra- through hexa-compounds and 50–90% of the hepta-CDD/CDF compounds present in the feed was eliminated in the feces, and 7–54% of all 2,3,7,8-substituted PCDDs/PCDFs was excreted in the eggs.[187] Adipose tissue was the major deposition site for the PCDDs/PCDFs, with less than 0.5% in the liver. BMFs between the soil and the adipose tissue ranged from ~8 for penta-CDDs/CDFs to 0.3 for octa-CDD/CDF.

Several studies have been conducted in which rodent or other small mammals were fed 2,3,7,8-TCDD-contaminated soil or extracts from soil. When results from these studies were compared,

large differences in 2,3,7,8-TCDD bioavailability were found. Soil obtained from two areas in Missouri — Times Beach and Minker Stout — was contaminated with approximately 800 ng/g 2,3,7,8-TCDD as a result of the improper use of waste oils for dust control. When the soil was administered to guinea pigs by gavage as an aqueous suspension, severe mortality occurred, with LD_{50} values close to the value for positive controls (1.75 μg/kg body weight).[188] Based on a comparison of liver concentrations in the positive controls and in the soil-treated animals, it can be calculated that ~85% of the 2,3,7,8-TCDD in the soils was bioavailable. In contrast, when guinea pigs were administered soil from a former 2,4,5-T manufacturing site in New Jersey, typical signs of PCDD toxicity were not found, and the calculated bioavailability was only 0.5%.[189] The soil for this study was contaminated with 2200 ng/g 2,3,7,8-TCDD and several other PCDD/PCDF compounds. Two explanations were offered for the observed differences in bioavailability. First, the nature of the soil could alter the bioavailability. The fill at the New Jersey site contained asphalt, and the carbonaceous nature of this matrix could enhance binding of PCDDs/PCDFs. Second, the soil at New Jersey was contaminated over a long period of time, with a generally aqueous medium, whereas the Missouri soils were contaminated with an oil mixture. The presence of oil would tend to reduce the binding of PCDDs/PCDFs to the soil and make them more bioavailable.

The potential for PCDD/PCDF bioaccumulation in ruminants in the wild may be assessed from results of a study on 2,3,7,8-TCDD bioaccumulation in beef cattle.[190] In this study, seven animals were fed a standard cattle ration containing 24 pg/g 2,3,7,8-TCDD for 28 days. Three animals were then sacrificed for tissue analysis, while 2,3,7,8-TCDD elimination in the remaining animals was monitored over a 36-week period by taking fat biopsies at 4-week intervals. The data were examined using a one-compartment kinetic model, and it was extrapolated that a steady-state level would be reached in 500 days, at which time the fat-tissue concentration would be 594 pg/g (all tissue concentrations of PCDDs/PCDFs reported in this subsection are expressed on a wet-weight basis unless noted otherwise). Therefore, a BMF of 25 could be expected for ruminant species in the wild such as deer. This value would be considerably reduced for does with fawns since the carry-over from feed to milk for cows was found to vary from 40% for 2,3,4,7,8-PeCDF to 0.68% for OCDD.[191] The excreted PCDDs/PCDFs would, however, increase the PCDD/PCDF body burden of the fawns.

18.3.2.2 Abiotic Dispersal of PCDDs and PCDFs

18.3.2.2.1 Atmospheric Dispersal of PCDDs and PCDFs

Studies carried out to determine the sources of PCDDs/PCDFs in the environment have revealed that the atmosphere is a very important medium for the transport of PCDD/PCDF compounds. With the exception of sediments collected from Lake Ontario, remarkable similarities were found between PCDD/PCDF patterns in urban-air particulates and in sediments from different locations in the Great Lakes.[192] The generalized pattern was dominated by octa-CDD, and it was suggested that atmospheric transport of combustion-derived PCDDs/PCDFs was the common source for each location. By invocation of photolysis as a plausible degradation pathway with the less-chlorinated PCDD/PCDF compounds, the PCDD/PCDF patterns found for municipal incinerators could be transformed into the patterns found in the sediments and the air particulates. In the case of the Lake Ontario sample, which had elevated concentrations of both octa-CDD and octa-CDF, a pattern-recognition technique showed that the sample had a PCDD/PCDF pattern very similar to the PCDD/PCDF pattern in pentachlorophenol. It is, in fact, known that chemical wastes have been transported from the Niagara River into Lake Ontario and that some of these wastes could have included pentachlorophenol and associated PCDDs/PCDFs. In another study of PCDD/PCDF deposition in sediment cores from the Great Lakes, it was determined that the most isolated Great Lake, Lake Superior, receives only 20% of its current input of PCDDs/PCDFs from local sources by atmospheric and aquatic routes. In contrast, Lake Ontario receives >90% of its input from local sources.[193]

A small lake from which sediments were collected, Siskiwit Lake, is situated on a remote island in Lake Superior; it therefore could receive contaminants only via atmospheric transport. By use of radiochemical techniques for dating sediment core sections, annual PCDD/PCDF fluxes to Siskiwit Lake could be plotted against time from 1920 to 1998.[194] It was found that the annual fluxes to the lake were low (< 1 pg/cm^2/year) before 1935 and then increased to a maximum of 9.5 pg/cm^2/year in the period 1975–1980. Since this increase parallels the increase in production of chlorinated aromatic compounds in the 1940s, it was concluded that combustion of wastes containing these compounds was the most significant source of atmospheric PCDDs/PCDFs. The decline in PCDD/PCDF concentrations that occurred after the 1970s was attributed to a reduction of particulate emissions following the passage of environmental legislation. However, the total decline for the period 1987–1995 was estimated to be 20%, whereas the U.S. EPA has calculated that emissions from combustion sources declined by 75% during the same time period. The lower-than-expected rate of decline of PCDDs/PCDFs in the sediments was attributed to the photochemical conversion of PCP to OCDD and HpCDDs in condensed atmospheric water (see below). Additional studies conducted on sediment cores collected from remote lakes in North America[195] and Europe[196–198] support the pattern of current and historical loading of PCDD/PCDF compounds described for Siskiwit Lake.

It is generally accepted that combustion processes are a major source of PCDDs/PCDFs in the environment. In contrast, a study conducted in 1995 found that, on a global scale, deposition estimates exceeded emission estimates by a factor of approximately four.[199] In this study, depositional fluxes were determined from the PCDD/PCDF concentrations in 107 soil samples. Total global deposition was estimated to be 13,100 ± 2,000 kg/yr. Data from air sampling conducted in the North Atlantic suggested that less than 10% of this total deposition was occurring over the oceans.[200] The deposition estimate was then improved by collection of 63 additional soil samples from areas that had been inadequately sampled in the first study.[201] Since NO_x emissions were highly correlated with PCDD/PCDF fluxes, available NO_x data were used to estimate PCDD/PCDF emissions in areas where no soil samples had been collected. The database for emissions estimates was further expanded after PCDD/PCDF emissions were found to be well correlated with both CO_2 emissions and Gross Domestic Product (GDP) of the country. Only 23 countries did not report data for either CO_2 or GDP, and these countries were at any rate considered to have very low dioxin emissions.[202] Through the use of all of these additional data, it was determined that global PCDD/PCDF emissions were in the range of 1800 kg/year, compared to a deposition estimate of 3,000–10,000 kg/year.[202] Therefore, although the more recent data show that the mass balance discrepancy may be closer to a factor of two, the findings still point to a deposition rate that exceeds the emissions rate.

Experiments conducted in the laboratory have shown that 1,2,3,4-TCDD can react in the gas phase with OH radicals generated from either the photolysis of ozone (O_3) in the presence of water or from the photolysis of hydrogen peroxide.[16] The 1,2,3,4-TCDD-OH reaction rate constant was calculated from experimental data, and the average OH reaction rate constants for PCDD/PCDF congener groups with four to eight chlorines were then calculated from structure–activity considerations. When these average OH rate constants were applied to source data via a simple model incorporating gas/particle partitioning, a reduction in concentrations of lower chlorinated congeners was found, but OCDD and HpCDD were not found to be as predominant as they are in sinks.[202]

In order to reconcile the mass balance data and the congener profile data for sources and sinks, Baker and Hites[202] have suggested that PCP is converted into OCDD and HpCDD by a photochemical reaction in condensed atmospheric water. In support of this hypothesis, it was found that aqueous solutions of PCP could be converted in a photochemical reactor into OCDD, HpCDD, and HxCDD at respective approximate yields of 0.1, 0.01, and 0.003%. Based on current measurements of PCP concentrations in rain, these yields would be sufficient to close the mass balance gap. While the experiments were conducted at environmentally relevant pH (5.5) and irradiation wavelengths

(> 290 nm), the authors have pointed out that the laboratory conditions do not mimic all of the conditions existing in condensed atmospheric water.

18.3.2.2.2 Aquatic Dispersal of PCDDs and PCDFs

The subject of aquatic dispersal of PCDDs/PCDFs has received considerably less attention than that of atmospheric dispersion. Tyler and co-workers[203] found that PCDD/PCDF concentrations in sediments from the Clyde Estuary decreased with distance downstream from Glasgow. The concentration at a 1-km distance was 6000 pg/g, decreasing to 322 pg/g at a distance of 22 km. Since organic pollutants favor fine sediments with high surface area and high organic carbon content, it was suggested that these fine sediments were being filtered out in their movement downstream, thereby resulting in a decrease in the PCDD/PCDF sediment concentration. However, there was also a decrease in the relative proportion of octa-CDD, suggesting that other physicochemical processes were occurring.

18.3.3 PCDD and PCDF Removal Processes in Aquatic Systems

Laboratory studies have shown that PCDDs/PCDFs dissolved in water can be photodegraded on exposure to either sunlight or UV light at wavelengths that are environmentally relevant (> 290 nm).[204,205] The process follows first-order kinetics, and the rates in sunlight are quite rapid for congeners dissolved in pure water (half-lives of 6.4 h and 8.3 h for 1,2,7,8-TCDD and 1,2,7,8-TCDF, respectively). When the PCDDs/PCDFs were dissolved in natural water from streams and lakes, they were photosensitized by humic acids and other organic compounds, increasing the photolysis rates by a factor of two.[15,204] While dechlorination occurs during these reactions to form lower-chlorinated PCDDs/PCDFs, the dechlorination process makes only a minor contribution to the total loss of the parent PCDD/PCDF.

Anaerobic microbial metabolism is another degradation process that has been shown to dechlorinate PCDDs/PCDFs in sediments.[206] In contrast to photodegradation reactions, in which the lateral positions are preferentially dechlorinated, peri positions (the position closest to the ether bridge) are frequently selected for dechlorination by anaerobic microorganisms. This could potentially increase toxicity by leading to the formation of 2,3,7,8-substituted congeners. However, over time, the 2,3,7,8-substituted congeners are subject to degradation by consortia with the capability of removing chlorine atoms from both lateral and peri positions. Studies carried out using sediment inocula from polluted rivers in the United States and Germany suggest that 20 to 30% of PCDDs/PCDFs are dechlorinated over periods varying from 7 months to 2 years during incubations at temperatures varying from 20°C to 30°C.[206-208] There is also evidence that PCDDs/PCDFs can be dechlorinated by abiotic processes involving electron transfer from inorganic (zerovalent iron and zinc) and organic (hydroquinone/quinone and vitamin B12) molecules.[209] Additional data show that peridechlorination may be enhanced by the synergistic actions of the abiotic and microbial dechlorination processes.[210]

While these laboratory studies indicate that PCDDs/PCDFs can be degraded by sunlight, anaerobic microorganisms, or abiotic dechlorination, it is not clear whether any of these degradation processes has a significant impact on the levels of PCDDs/PCDFs in the aquatic environment. Since PCDDs/PCDFs are hydrophobic compounds, they are primarily associated with sediment particles; this association would limit the dissolved concentrations of the compounds available for photodegradation. In the case of anaerobic metabolism, dechlorination rates for OCDD in sediment systems were considerably lower than those found using spiked sediment-free elutriates.[211] Therefore, bioavailability to microorganisms from sediments could be a limiting factor in the anaerobic metabolism of PCDDs/PCDFs. Finally, the anaerobic incubations were carried out in the presence of cosubstrates and nutrients and at temperatures exceeding those generally found in the aquatic environment.

18.4 AMBIENT LEVELS OF PCBs

18.4.1 Ambient Levels of PCBs in Aquatic Biota

One of the first reports of the environmental persistence of PCB congeners came from the observation of a Swedish chemist, Sören Jensen, who noted their presence in fish. He was looking for evidence of DDT contamination in biological tissues and discovered, in addition to DDT and its metabolites, several other chlorinated hydrocarbons, which were later verified to be chlorinated biphenyls.[212] As accumulators of PCBs, many organisms are among the best monitors of PCB, especially for conducting trend analyses. They integrate exposure over extended time periods, and, since they magnify levels, their concentrations will build up to levels much higher than in their external media, allowing for ease of measurement. Several nations have monitoring programs underway involving analyses of PCBs in sentinel species, usually fish,[29] but also aquatic birds (herring gulls),[36] marine mammals,[213] and shellfish.[214] In the Great Lakes, lake trout have been routinely monitored since 1979; in them, a continuing decline in PCBs has been reported.[36] NOAA Status and Trends data exist for PCBs in coastal areas also showing downward trends of PCBs in mussels.[214] European data, especially from Sweden, have been discussed in several publications, and both terrestrial and aquatic species have been studied.[215] Especially high levels have been reported in porpoises and seals, and several long-term studies have been done on polar bears.[215]

18.4.2 Ambient Levels of PCBs in Sediments

Much of the PCBs released into the environment over time are believed to reside in sediment. As clean sediment is delivered (now that external loadings have decreased) these deposited sediments are being buried, and eventually, in the absence of scouring or resuspension, they will be removed from the MER of PCBs. Deviations from this gradual burial process have been documented. In a Lake Erie study of PCBs in biota, investigators found that unusually high wind speeds from 1996 to 1997 led to increased PCB concentrations in biota that reside above the sediment due to resuspension of previously buried sediment deposit.[217] Therefore, deep scouring during flooding in rivers or heavy-storm-induced resuspension in lakes can lead to renewed exposure of PCBs from sediment deposits.

Other additional natural losses such as microbial degradation are also possible, but the rates of such processes in deeper sediments are very slow. Historical assessments of PCB deposition into sediments rely on dating the deposition layers within sediment cores that are removed from the deposit areas and relating the layers with their respective PCB concentrations. The chronology of past depositions of the PCB into undisturbed sediments has been documented for the Hudson River estuary, Great Lakes, and the Baltic.[217–220] Several sediment profiles have provided evidence for anaerobic dechlorination losses, for example, in the Hudson River[121] and in the tributary basin of the Thames River in England.[221] These researchers' evidence for dechlorination was expressed as a change in the ratios of less highly chlorinated (tri- and tetra-) congeners relative to congeners with five or more substituted chlorine atoms. In one of their cores samples, they[221] reported an average ratio of 0.23 from the surface of this core to ratios increasing to 0.32 at 2.3 m depth and finally to 0.62 by 5.8 m below the surface. As long as contaminated sediments reside in place in deposit zones they are subject to remobilization. Careful stewardship of these deposit zones is the preferred option. This stewardship is best provided by careful removal and placement in secure upland disposal facilities. While choosing this option has to be done on a case-by-case basis, it is the most frequently chosen option when costs are not a concern.[39]

18.4.3 Ambient Levels of PCBs in Soils

There are few data on the levels of PCBs in soil. The general rule is that ambient air levels of PCBs are greatly affected by soil/air partitioning and that soils and other exposed surfaces in urban

communities generally receive influx of atmospheric PCBs. However, now that ambient background levels of PCBs in air are declining, soils in rural areas are releasing more PCBs than they are receiving. Thus, the congener ratios of PCBs in rural soils and at remote sites tend to reflect depletion of the more volatile congeners and enrichment of more highly chlorinated congeners.[96] In tests of several soil types by Ayris and Harrad,[107] the most important influences on the rate constant for soil partitioning were from the log $K_{octanol/air}$ (adjusted for soil temperature) and soil organic carbon.

One of the more careful and complete studies of soil interactions with PCBs has been conducted by Kevin Jones' research group in the United Kingdom.[56,98,222,223] Most of the soils that were the centerpiece of their work came from agricultural plots. The levels of total PCBs ranged from 10 to 670 μg/kg (median 30 μg/kg).[222] Twenty-six congeners were routinely monitored and quantitated in each of the samples. The soils included contemporary samples and historical samples dating back to 1944. All of the contemporary samples had levels similar to those in early 1940s samples; however, there tended to be a higher proportion of more highly chlorinated congeners in the contemporary samples. The soil levels of PCBs increase when atmospheric levels are high by gas-to-soil exchange. Then, as source releases are depleted, the exchange from surface soils is reversed, buffering the levels in the atmosphere.[98] There appears to be a delay (10 years' time lag was observed by Harner and co-workers[98]), and there is a slower release of those accumulated PCBs having half-lives of 10–20 years, an effect that tends to prolong background levels for longer periods of time. Numerous investigators have noted that hotspot buildup often occurred in soils near transformer spills; these remain for long periods of time.

18.4.4 Ambient Levels of PCBs in Air

Air concentrations of total PCBs in metropolitan centers generally run about five to ten times higher than background levels and correlate closely with the higher particle concentrations in cities. The total gaseous PCB concentrations at an overlake site 15 km from Chicago ranged from 132 to 1120 pg/m,^{3} with higher concentrations occurring in warm periods and when wind directions were from the city. Therefore, Chicago was determined to be a major source of PCBs for Lake Michigan.[86] Because of concern for elevated concentrations of PCBs in the Great Lakes region and because of the sensitivity of this area to PCBs, there is currently an air-monitoring network analyzing PCBs on a regular basis (IADN Network-Integrated Atmospheric Deposition Network).[224,225] Data now available from these collections show that mean yearly values for PCBs range from 89 to 370 pg/m.^{3} Concentrations at an urban site near Lake Erie were about two times higher than concentrations at the two more remote sites near Lake Superior.[226]

Five years of data, from 1992 to 1997, were summarized for PCBs measured in air at a site in northwest England. PCB levels declined, with specific half-lives ranging from 2 to 6 years for all of the congeners that were modeled; the decline was fastest for congener 52.[56] Schreitmueller and Ballschmiter[85] measured PCBs in air over the North Atlantic. Values for total PCBs ranged between 48 pg/m^3 in 1992 in the eastern North Atlantic and 22 pg/m^3 in the central South Atlantic for this year. Several papers confirm that PCB air concentrations vary with season (high concentrations when air temperatures are high and low PCB concentrations when the temperatures are lower). PCB concentrations in air vary with latitude, i.e., they are higher at mid latitudes (most industrial sources exist here) and lower at higher latitudes that are closer to polar regions.[55]

18.5 AMBIENT LEVELS OF PCDDs AND PCDFs

18.5.1 Ambient Levels of PCDDs and PCDFs in Aquatic Biota

When the first efforts to monitor PCDDs/PCDFs were undertaken in the 1980s, major emphasis was placed on the determination of 2,3,7,8-TCDD in fish from aquatic environments that receive

wastes from industrial processes. In 1983, O'Keefe and co-workers[227] found that 2,3,7,8-TCDD was present in fish from all of the Great Lakes. However, the most heavily contaminated fish were found in Lake Ontario and in the Saginaw Bay area of Lake Huron, where concentrations varied from 2 to 162 pg/g and from 2.5 to 29 pg/g, respectively. Fish from the other Great Lakes (Lake Erie, Lake Michigan, and Lake Superior) had < 3pg/g. Later studies[228–230] confirmed these results. Norstrom and co-workers[231] also found that herring gull eggs collected from colonies in Lake Ontario and the Saginaw Bay area of Lake Huron had higher 2,3,7,8-TCDD concentrations (43 to 86 pg/g) than did eggs from colonies in Lakes Erie, Michigan, and Superior (9 to 11 pg/g). PCDDs/PCDFs containing from four to eight chlorine atoms were determined in Great Lakes fish by Stalling and co-workers[232] in 1982 and Zachareweski and co-workers[233] in 1989. Both studies showed that PCDFs were more widely distributed in the Great Lakes than were PCDDs, which suggests that the PCDFs are entering the lakes from other sources, including commercial Aroclors. The major PCDD/PCDF congener in most samples was 2,3,7,8-TCDF, with the exception of samples from Lake Ontario, where 2,3,7,8-TCDD was the major congener, and samples from Saginaw Bay, Lake Huron, where there were significant quantities (> 30 pg/g) of tetra-, penta-, and hexa-CDDs and CDFs.[232] While fish collected from Lake Michigan generally have low concentrations of PCDDs/PCDFs, higher concentrations have been found in biota collected around Green Bay, WI, an area contaminated by effluents from pulp and paper mills and other industrial wastes. Eggs from colonies of Forster's terns located in this area were found by Kubiak and co-workers[234] to contain median 2,3,7,8-TCDD and total PCDD concentrations of 37 and 102 pg/g, respectively.

A national survey conducted by the U.S. EPA demonstrated that contamination of aquatic biota in the U.S. by PCDD/PCDF compounds was not confined to the Great Lakes. In this study, bottom-feeding and predator fish were collected from almost 400 sites including the Great Lakes. It was found that 2,3,7,8-TCDD could be detected in fish from 112 of the 395 sites (28%), with concentrations below 5 pg/g from 74 sites (67%), between 5 and 25 pg/g from 34 sites (32%), and between 25 and 85 pg/g from 4 sites (1%).[137]

Aquatic biota, other than fish and birds, bioaccumulate PCDDs/PCDFs. Bullfrogs (*Rana catesbeiana*) collected near a chemical plant at Jacksonville, Arkansas, that formerly manufactured the herbicide 2,4,5-T had concentrations of 2,3,7,8-TCDD in their fat tissues as high as 68,000 pg/g.[235] For females, concentrations were also elevated in ovaries and oviducts. Snapping turtles (*Chelydra serpentina*) are long-lived organisms consuming both plants and animals, including fish; they therefore tend to bioaccumulate high concentrations of organochlorine compounds. Ryan and co-workers[236] analyzed PCDD/PCDF compounds in fat and liver samples from three snapping turtles from the upper St. Lawrence River. Concentrations of 2,3,7,8-TCDD in the fat tissue varied from 232 to 474 pg/g. It is conceivable that this PCDD congener was transported into the upper St. Lawrence from its source, Lake Ontario. One of the three samples was collected near industrial sites at Massena, New York; this sample contained 3 ng/g 2,3,4,7,8-penta CDF in addition to 2,3,7,8-TCDD. It is now known that this area is heavily contaminated with PCBs and PCDFs.

The aquatic species described above accumulate predominantly 2,3,7,8-substituted isomers. However, crustaceans discriminate to a lesser extent between 2,3,7,8-substituted and non-2,3,7,8-substituted isomers, as was shown in a study conducted by Rappe and co-workers[237] in the New York Bight and the Newark Bay area of New York Harbor. When tissues of blue crabs (*Callinectes sapidus*) and American lobsters (*Homarus americanus*) were analyzed, concentrations were considerably higher in the hepatopancreas than in the meat, with a concentration of over 6000 pg/g 2,3,7,8-TCDD in the hepatopancreas from one crab. While 2,3,7,8-TCDD was the major TCDD isomer, the 2,3,7,8-substituted isomers constituted less than 30% of the total congener group concentrations for the penta- and hexa-CDDs and the tetra- to hexa-CDFs. In general, similar isomer patterns were found in the hepatopancreas and the meat tissue.

In Europe, studies to monitor PCDDs/PCDFs in aquatic biota have focused on major rivers, such as the Rhine and the Elbe, and on the Baltic Sea. In the Elbe, bream (*Abramis brama*)

collected in the Hamburg Harbor area near a pesticide manufacturing plant had total 2,3,7,8-substituted PCDD/PCDF concentrations and 2,3,7,8 TCDD concentrations as high as 308 and 102 pg/g, respectively.[238] Lower PCDD/PCDF concentrations (< 50 pg/g) were generally found in bream collected at other locations in Hamburg Harbor and at sampling points from the river mouth to a point 200 km upstream.[239] In all of the samples in this study, the PCDF concentrations exceeded those of PCDD, with 2,3,7,8-TCDF/2.3,7,8-TCDD ratios exceeding 10. Also, comparable levels of 1,2,3,7,8- and 2,3,4,7,8-penta CDF were detected, whereas in both North American and Scandinavian studies the 2,3,4,7,8 isomer has been found to predominate. However, it was also apparent that the capillary gas chromatography column was not capable of separating 1,2,3,7,8-and 2,3,4,7,8-penta CDF standards. Concentrations and isomer patterns of PCDDs/PCDFs in fish from the upper reaches of the Rhine and its tributary, the Neckar, were comparable to those found in the River Elbe fish. The more usual pattern of higher 2,3,4,7,8-penta CDF than 1,2,3,7,8-penta CDF concentrations was found in the Rhine/Neckar samples.[240] Eel samples, however, had quite different patterns that were dominated by octa-CDD, suggesting a more direct influence from sediments.

In 1989, Rappe and co-workers[241] summarized their investigations of PCDD/PCDF concentrations in fish collected from the Baltic Sea and from Lake Vattern in Sweden. Composites of herring from various locations in the Baltic and a control site on the Atlantic coast of Sweden had very similar PCDD/PCDF patterns that were dominated by 2,3,4,7,8-penta CDF (3–19 pg/g), with lower amounts of 2,3,7,8-TCDF (1.7–6.2 pg/g) and no detectable levels of 2,3,7,8-TCDD. Total congener group concentrations varied from 7 pg/g for the Atlantic Coast sample to over 30 pg/g for a sample collected near Stockholm, with intermediate levels for samples from the Gulf of Bothnia, an area in which several pulp and paper mills are located. As salmon are predators, it was not unexpected to find higher PCDD/PCDF concentrations in these fish than in either herrings or hatchery-raised salmon receiving synthetic food. Wild salmon from the Gulf of Bothnia had PCDD/PCDF concentrations approximately five to ten times higher than either the herrings or the hatchery salmon. In samples collected close to pulp and paper mills, the dominant PCDD/PCDF congener was either 2,3,7,8-TCDD, as in the case of perch from Norrsundet in the Gulf of Bothnia (13–19 pg/g), or 2,3,7,8-TCDF for Artic Char from Lake Vattern (20–75 pg/g). For the Artic Char, there was a direct relationship between fish weight and contaminant levels.

Monitoring data are now available showing the time trend of PCDD/PCDF concentrations in aquatic biota. For herring gull eggs from the Great Lakes, concentrations declined between 1981 and 1984.[242] However, there were no obvious temporal trends between 1984 and 1991. In a review of a database on TCDD concentrations in fish and shellfish collected from U.S. waterways between 1979 and 1994, Firestone and co-workers found that there had been a steady decline during the study period.[243] This decline was most apparent at contaminated sites on the Great Lakes. From 1981 to 1982, five of ten fish collected in Lake Ontario had TCDD concentrations exceeding 11 pg/g, whereas in 1994, TCDD was not detected in any of nine fish (≤1–2 pg/g). Significant declines in PCDD/PCDF levels in wildlife have also occurred in British Columbia, Canada as a result of the replacement of chlorine by chlorine dioxide as a bleaching agent for wood pulp and the introduction of regulations to control the use of chlorophenols as antisapstaining agents for undried lumber. In a study of PCDDs/PCDFs in osprey eggs collected in the drainage systems of the Columbia and Fraser Rivers, reductions between four- and tenfold were found in the PCDD/PCDF concentrations in the eggs over the period from 1991 to 1997. These reductions were mainly attributed to regulatory controls on PCDD/PCDF releases from pulp and paper mills introduced between 1991 and 1993.[146,244] However, in many recently industrialized countries and in Central and Eastern European countries, reports published between 1995 and 1997 show that there are locations where wildlife are still contaminated with high concentrations of PCDDs/PCDFs. Fish taken from the Er Jen River in Taiwan, near metal-reclamation plants, had PCDD/PCDF TEQs as high as 2084 pg/g.[245] Blubber tissue from one juvenile and two adult female Baikal seals (*Phoca sibirca*) collected from Lake Baikal in Russia had PCDD/PCDF TEQs of 28, 73, and 93 pg/g,

respectively — levels comparable to those found for ringed seals (*Phoca hispida*) in contaminated areas of the Baltic Sea.[246]

18.5.2 Ambient Levels of PCDDs and PCDFs in Sediments

Current background PCDD/PCDF concentrations in sediments from various countries in the Northern Hemisphere have been determined from analysis of the top sections of sediment cores from remote lakes. Between 1993 and 1998, it was reported that Siskiwit Lake in the United States,[194] Loch Coire nan Arr in northwest Scotland,[196] and three lakes in Subarctic Finland[197] had recent total PCDD/PCDF sediment concentrations of 382, 488, and 202 ± 92 pg/g, respectively. These data are in remarkable agreement and demonstrate that long-range atmospheric transport can distribute PCDDs/PCDFs over wide areas. Lakes in the Black Forest in Germany, where the prevailing winds can transport PCDDs/PCDFs directly from emission sources in industrial areas, have higher sediment PCDD/PCDF concentrations (8.9–18 ng/g).[198] The highest sediment PCDD/PCDF concentrations occur where there is direct loading to water from point sources. Norwood and co-workers[247] analyzed surface sediments from a number of contaminated coastal areas in the United States and found the highest PCDD/PCDF concentration (44 ng/g) in sediment from Eagle Harbor, Washington, a location that had been contaminated with PCP wastes.

18.5.3 Ambient Levels of PCDDs and PCDFs in Soils

Comprehensive studies of PCDD/PCDF contamination in soil samples have been carried out in England. The first study involved the collection of 77 rural soil samples at the intersection points of a 50-km grid.[248] When 12 samples contaminated by local point sources were eliminated from the data set, it was found that the mean concentrations of PCDDs and PCDFs were 311 and 132 pg/g, respectively. Mean concentrations of the PCDDs/PCDFs were considerably higher in soil samples collected from 19 urban areas (11 ng/g for PCDDs and 0.9 ng/g for PCDFs).[249] Principal-components analysis suggested that combustion processes, such as coal burning and municipal incinerators, were the principal sources of PCDD/PCDF compounds in the urban soils. In an investigation of PCDDs/PCDFs in soil samples collected in rural Germany, samples collected from cultivated land and grassland had total PCDD/PCDF concentrations slightly lower than those found in the English study (mean values of 123 pg/g and 170 pg/g for cultivated land and grassland, respectively).[250] However, elevated PCDD/PCDF concentrations were found in soil samples collected from forested areas (mean values of 2.3 ng/g and 6.5 ng/g for deciduous and coniferous forest soils, respectively). It is known that leaves and needles can take up PCDDs/PCDFs, primarily by dry gaseous deposition, and subsequently the falling needles/leaves increase PCDD/PCDF concentrations in the surrounding soil.[251]

18.5.4 Ambient Levels of PCDDs and PCDFs in Air

Measurements of PCDD/PCDF compounds in ambient air have been carried out at several locations in Europe, North America, New Zealand, and Japan. In rural areas,[168,252] total PCDD/PCDF concentrations in ambient air generally do not exceed 1 pg/m^3 and are often lower (< 0.5 pg/m^{12}).[253] In suburban locations, where there is no impact from point sources, PCDD/PCDF concentrations range from 1 to 5 pg/m^3.[254] Urban-air concentrations of PCDDs/PCDFs range from 5 to 20 pg/m,^{3} but concentrations can exceed 100 pg/m^3 where there is a direct impact from industrial emissions.[252] PCDD/PCDF patterns in ambient-air samples from different locations are usually quite similar, with equal amounts of PCDDs and PCDFs. The congener profiles are dominated by 2,3,7,8-TCDF and octa-CDD. The decline in deposition fluxes following the introduction of pollution-control

regulations has been discussed previously in this chapter. This decline has also been reflected in ambient-air PCDD/PCDF concentrations, particularly in urban areas. In the German cities of Köln, Duisburg, Dortmund, and Essen, ambient PCDD/PCDF concentrations were in the range of 6.5–17.4 pg/m^3 in 1987/1988; these levels had declined to 3.2–9.9 pg/m^3 by 1993/1994.[254]

18.6 EFFECTS OF PCBs, PCDDs, AND PCDFs

Most of the data describing the ecological effects of PCBs, PCDDs, and PCDFs in the environment deal with direct aquatic exposures (sediments/particulates, food, and water) and, thus, their related aquatic-based foodchains. Over time, especially in the last 20 years, additional toxicological and exposure information has been generated on aquatic species, especially predators, including other aquatic species, terrestrial and marine mammals, and avian species. Before the advent of improved analytical capabilities and availability of standards of the specific congeners of the PCBs, data on toxicity were only available for the commercial mixtures.

Evaluation of the health effects of PCBs is complicated by several factors. Worldwide, each of the commercial PCBs is a mixture of fewer than the possible 209 congeners, and toxicity depends on the precise congener makeup of each of these mixtures that accumulate in the tissues of organisms and the metabolites that arise from these residues. Also, the degree of contamination of commercial PCB mixtures with PCDFs complicates the situation, since PCDFs are considerably more toxic, especially to fish. Furthermore, direct transfer of the unaltered manufactured PCB mixtures to a target organism seldom occurs, except in a laboratory situation. Even then, congener and mixture homolog group patterns change following assimilation due to differential metabolism in various test species. This holds true in the ambient environment as well, where multiple processes change composition and relative proportions of congeners. Of the PCDDs and PCDFs, those that are bioaccumulated and biomagnified are primarily 2,3,7,8-substituted. For PCBs, both dioxin-like and nondioxin-like congeners bioaccumulate and biomagnify in organisms and produce acute and chronic effects.

The earliest tests were done with Aroclor mixtures. Table 18.4, compiled from ATSDR's Toxicological Profile for Polychlorinated Biphenyls,[27] provides an example of these mixture tests, predominantly done for human-health purposes. The lethal dose decreases with length of exposure, and the most serious damage to these organisms occurs through reproductive effects. Reproductive effects occur at doses much lower than mortality levels.

Regulations for PCBs are based on total PCB concentrations (e.g., a sum of the mixed congeners), while PCDD/PCDF regulatory guidelines require individual congener identification and quantification. Mechanistically, this has resulted in an interpretation gap between the PCBs and PCDDs/PCDFs. While specific isomer information has always been available for assessing exposure and toxic dose for PCDD/PCDFs, concentration data for PCBs has always been more complicated to deal with, e.g., even with the congener-specific data for PCBs there is currently no unified and accepted way to integrate all of the multiple congener exposures.

18.6.1 Toxicological and Structural Similarities

The general consensus about the mode of action of TCDD is that it involves the activation of the TCDD-receptor complex, and the subsequent translocation of this complex into the cell nucleus is a necessary, but not sufficient, prerequisite for any TCDD-related effect.[255] It is also generally agreed that: (1) animals that possess an aryl hydrocarbon (Ah) receptor respond to TCDD similarly; (2) multiple effects, including enzyme induction, immunotoxicity, reproductive toxicity, developmental toxicity and carcinogenicity, occur in all susceptible species; and (3) chemicals that are

Table 18.4 Most Sensitive Laboratory Animal Species Tested with Mixed Aroclors

Response	Species	Route[b]	Exposure Duration/ Frequency	NOAEL[c] (mg/kg/day)	LOAEL (effect)[d] (mg/kg/day)	Form
			Acute Exposure			
Death	Rat	GO	One time	—	1010 to 4250 (LD_{50})	Mixed
Death	Mink	G	One time	—	750; 4000 (LD_{50})	Mixed
Death	Mouse	PCDF	2 weeks	—	130 (LD_{50})	A-1254
Reproductive	Rat	GO	9d	8	32	A-1254
			Intermediate			
Death	Rat	PCDF	8 months		72.4 (80% mort.)	A-1260
Death	Rat	GO	2.5 weeks	—	840 (13% lower surv.)	A-1260
Death	Mouse	PCDF	6 months	—	48.8 (lower surv.)	A-1221
Death	Monkey	PCDF	2 months	—	4 (near 100% mort.)	A-1248
Death	Mink	PCDF	28–4 months	8	1.9–7.1 (LD_{50})	A-1254
Reproductive	Rat	GO	1 months	—	30	A-1254
Reproductive	Mouse	PCDF	108 days	1.25	12.5	A-1254
Reproductive	Monkey	PCDF	7 months	—	0.2	A-1248
Reproductive	Monkey	PCDF	2 months	—	4.3	A-1248
Reproductive	Mink	PCDF	4–8 months	0.1 to 0.2	0.4 to 0.9	A-1254
			Chronic			
Death	Rat	PCDF	205 weeks	—	2.5 (lower surv.)	A-1254
Reproductive	Monkey	PCDF	16 months	0.008	0.03	A-1016
Cancer	Rat	PCDF	14–24 months	—	1.25 to 5	A-1254;1260

[a] Compiled from ATSDR 1997[27] Toxicological Profile for Polychlorinated Biphenyls (Update) U.S. Department of Health and Human Services, Public Health Service, Washington, D.C., 1997, 429.
[b] Route of exposure, (GO) = gavage, oil; (G) = gavage; (PCDF) = food.
[c] NOEL = no observed effect level.
[d] LOEL = lowest observed effect level.

isostereomers of TCDD (i.e., polychlorinated and polybrominated dibenzo-*p*-dioxins, dibenzofurans, and coplanar biphenyls) act through the same mode of toxic action. This final point is used to justify discussing the mammalian and nonmammalian vertebrate effects of 2,3,7,8-substituted PCDDs and PCDFs together with the effect of coplanar PCBs.

Species-specific factors, such as uptake, disposition, and metabolism of TCDD, as well as interspecies differences in concentration, tissue distribution, and ligand affinity of the Ah receptor, all likely play roles in determining the relative sensitivity of an organism to TCDD. However, the presence of the Ah receptor clearly appears to be a necessary prerequisite for TCDD (and related compounds) to exhibit toxicity. The presence of the Ah receptor in fishes and the lack of the receptor in aquatic invertebrates are consistent with the relative sensitivities of the two groups of species to TCDD and structurally similar compounds. For example, TCDD has been shown to be lethal to a number of fish species when administered through the diet or the water, or by injection (egg or whole organism). Conversely, long-term exposures of a number of different species to TCDD (snails [*Physa* sp.], worms [*Paranais* sp.], and mosquito larvae [*Aedes aegypti*]) failed to result in discernible toxicity.[256]

Congener-specific chemistry advances and toxicological interpretation considerations have consistently driven the need for a normalization protocol based on common mechanisms of action. Today, this protocol is termed Toxicity Equivalency and is now commonly used in risk assessment. However, it is not yet a uniform regulatory requirement, at least in the United States.

For those congeners belonging to this group (all PCDDs, PCDFs and selected planar PCB congeners, Table 18.5), relative toxicity of a congener can be normalized to the potency 2,3,7,8-

TCDD, the prototype, and the most toxic compound of this group of stereoisomers. This normalized value is referred to as the TCDD toxicity equivalent concentration. Considered within a generally accepted model of additivity, these congeners' individual toxicity equivalent concentrations (actual concentration × Toxicity Equivalency Factor, or TEF) are summed to derive a total value of exposure in an organism of interest or in the foods that it consumes.

Table 18.5 World Health Organization Toxic Equivalency Factors (TEFs) for Humans Mammals, Fish, and Birds[260]

Congener	TEF		
	Humans/Mammals	Fish[a]	Birds[a]
2,3,7,8-TCDD	1	1	1
1,2,3,7,8-PentaCDD	1	1	1[b]
1,2,3,4,7,8-HexaCDD	0.1[a]	0.5	0.05[b]
1,2,3,6,7,8-HexaCDD	0.1[a]	0.01	0.01[b]
1,2,3,7,8,9-HexaCDD	0.1[a]	0.01[c]	0.1[b]
1,2,3,4,6,7,8-Hepta CDD	0.01	0.001	<0.001[b]
OctaCDD	0.0001[a]	<0.0001	0.0001
2,3,7,8-TetraCDF	0.1	0.05	1[b]
1,2,3,7,8-PentaCDF	0.05	0.05	0.1[b]
2,3,4,7,8-PentaCDF	0.5	0.5	1[b]
1,2,3,4,7,8-HexaCDF	0.1	0.1	0.1[b,d]
1,2,3,6,7,8-HexaCDF	0.1	0.1[d]	0.1[b,d]
1,2,3,7,8,9-HexaCDF	0.1[a]	0.1[c,d]	0.1[d]
2,3,4,6,7,8-HexaCDF	0.1[a]	0.1[d,e]	0.1[d]
1,2,3,4,6,7,8-HeptaCDF	0.01[a]	0.01[e]	0.01[e]
1,2,3,4,7,8,9-HeptaCDF	0.01[a]	0.01[c,e]	0.01[e]
OctaCDF	0.0001[a]	<0.0001[c,e]	0.0001[e]
3,4,4',5-TetraCB (81)	0.0001[a,c,d,e]	0.0005	0.1[c]
3,3',4,4'-TetraCB (77)	0.0001	0.0001	0.05
3,3',4,4',5-PentaCB (126)	0.1	0.005	0.1
3,3',4,4',5,5'-HexaCB (169)	0.01	0.00005	0.001
2,3,3',4,4'-PentaCB (105)	0.0001	<0.000005	0.0001
2,3,4,4',5-PentaCB (114)	0.0005[a,d,e]	<0.000005[e]	0.0001[g]
2,3',4,4',5-PentaCB (118)	0.0001	<0.000005	0.00001
2',3,4,4',5-PentaCB (123)	0.0001[a,d]	<0.000005[e]	0.00001[g]
2,3,3',4,4',5-HexaCB (156)	0.0005[d,e]	<0.000005	0.0001
2,3,3',4,4',5'-HexaCB (157)	0.0005[d,e]	<0.000005[d,e]	0.0001
2,3',4,4',5,5'-HexaCB (167)	0.00001[a]	<0.000005[e]	0.00001[g]
2,3,3',4,4',5,5'-HeptaCB (189)	0.0001[a,d]	<0.000005	0.00001[g]

Abbreviations: CDD, chlorinated dibenzodioxins; CDF chlorinated dibenzofurans; CB chlorinated biphenyls; QSAR, quantitative structure-activity relationship.

[a] Limited data set
[b] *In vivo* CYP1A induction after *in ovo* exposure
[c] *In vitro* CYP1A induction
[d] QSAR modelling prediction from CYP1A induction (monkey, pig, chicken, or fish)
[e] Structural similarity
[f] No new data from 1993 review (1)
[g] QSAR modelling prediction from class specific TEFs

Source: Van den Berg, M. et al., *Environ. Health Perspect.*, 106, 775, 1998. With permission.

The mechanism of action of all planar halogenated hydrocarbons (another designation for the group to which PCDDs and PCDFs and selected PCB congeners belong) is of great importance because the cumulative risks are much greater than their individual toxicities in many instances. Support for this approach was most recently documented by van den Berg and co-workers[257] under the auspices of the World Health Organization. This group reviewed previous work regarding TEFs

derived from mammalian species[258, 259] and recommended the establishment of animal-class-specific TEFs for humans/mammals, fish, and birds. The WHO database used to develop these TEFs is available from a U.S. Fish and Wildlife website[260] by clicking on dioxin_information.xls on the cited webpage. Table 18.5 provides a summary of these TEFs.

Most of the effort to isolate these more toxic components has focused on the dioxin-like response from PCBs. This similarity in effect to dioxin, i.e., mixed-function oxidase (MFO) induction, subcutaneous edema, reproductive impairment, weight loss, immune suppression, and hormonal alterations, has now further been narrowed to those compounds in the PCB mix that have a three-dimensional similarity in their structure. The potency and specificity for binding to the Ah receptor, followed by MFO induction (and correlatively, for potential toxicity) of individual PCB congeners can be directly related to how closely they approach the molecular spatial configuration and distribution of forces of 2,3,7,8-TCDD. The most toxicologically active PCB congeners are those having chlorine substitution at the *para* (4 and 4') positions and at least two *meta* (3,3',5,5') substitutions on the biphenyl nucleus, but no *ortho* (2,2',6, and 6') substitutions. The PCB congeners that have no *ortho* substitutions can assume a coplanar configuration, because the *ortho* chlorines are absent that would otherwise prevent rotation of the two opposing phenyl rings from assuming a planar configuration. Because the potential toxicity is enhanced by coplanarity, this rule limits the number of such PCB congeners to four: 77, 81, 126, and 169 (3,3',4,4'-, 3,4,4',5-, 3,3',4,4',5-, 3,3',4,4',5,5'). With the exception of number 81, the non*ortho*-coplanar congeners are potent inducers of aryl hydrocarbon hydroxylase AHH and 7-ethoxyresorufin O-deethylase EROD in *in vitro* rat hepatoma cell preparations. The 81 congener is a very potent avian *in ovo* EROD inducer (see Table 18.5). Virtually no toxicity data are available for this congener. The *in vitro* inductions are correlated with *in vivo* demonstrations of mammalian, avian, and fish toxicity such as thymic atrophy and inhibition of body weight gain.[261] The 81 congener has what is called a "mixed" type response in that it induces both methyl cholanthrene (3-MC)-type reactions and also phenobarbitol (PB)-type enzyme systems. From the data of Tillitt and co-workers[262] regarding mink accumulation and *in vitro* data, PCB 81 appears to be rapidly hydroxylated and is not biomagnified in mammals, but it is present in fish and birds as well as in their egg yolks, which contain lipids. It has not been reported or assessed in terms of human exposures.[263]

The second group of congeners having enzyme-inducing potencies and potential toxicities of high concern are analogs of the four non*ortho*-coplanar congeners that are still relatively coplanar but have a singe *ortho*-chloro substitution. These are congeners 105, 114, 118, 123, 156, 157, 167, and 189. This group of congeners has demonstrated mixed phenobarbitol (PB-)- and 3-methyl cholanthrene (3-MC)-type-inducing properties. Most of the more highly chlorinated dioxins and furans have received relatively little toxicity testing relative to 2,3,7,8-TCDD. Even the TEFs for the pentachloro dioxin and furan analogs are not based on whole-organism toxicity testing but on *in vivo* or *in vitro* MFO induction or quantitative structure–activity relationships (see footnotes in Table 18.5). In fish and birds, most PCDDs and PCDFs have not been reported in the primary literature with *in ovo* data for toxicity, and again the listed TEFs rely more on MFO induction data rather than data sets involving more thorough toxicity screening. However, older data on lethality and developmental anomalies for other PCDDs and PCDFs from the U.S. Food and Drug Administration (FDA) (reported by Verret,[264] and a Verret personal communication cited in Goldstein[265]) are generally consistent with the WHO TEFs for birds. This pioneering work by the FDA is now viewed as having been crucial to stimulating and refining scientific understanding of toxicity effects in birds and other oviparous vertebrates. For instance, the derivation of the WHO TEFs for birds and fish is *in ovo* tissue/residue-based, when such information is available. This stands in contrast to the situation for mammalian TEFs, which are derived from studies of adult dosing with concurrent partial metabolic elimination — despite the acknowledgment that body-burden-based toxicity information is preferable.

18.6.2 Structural and Toxicological Dissimilarities

Environmental exposures to PCB congeners and their metabolites that are not mechanistically identical to the PCDDs and PCDFs should still be considered. At a minimum, use of total PCB measurements in the assessment of the compounds' nondioxin-like effects is still prudent until similar equivalency approaches for other PCB congener groups having other modes of action are developed. This approach also provides a framework for interpreting long-term trends in environmental matrices. Giesy and Kannan[266] recently provided a perspective on the relative risks of dioxin-like vs. nondioxin-like PCBs using mink as a model species. Besides this example, little work has been done to assess the effects of the complex mix of dioxin-like and nondioxin-like congeners with their metabolites and across multiple animal classes.

Certain PCB metabolites have been found that may be operating via non-Ah receptor mechanisms or that may provide additional physiologically significant interactions with parent congeners. This fact is a caveat against pursuing only one approach,[268–271] despite the current evidence supporting the dominant toxicological importance of those congeners that act through the Ah-receptor. Conversely, it would be scientifically unsound to disregard the power of the TEF/TEQ approach and not to use it for ecological risk assessment. Based on what is known today, the uncertainties of continuing the present practice of assessing TCDD alone, or using TEQs for the PCDDs and PCDFs when considering total PCBs separately, would be greater than the uncertainty of adopting a TEF/TEQ approach that integrates PCDDs and PCDFs with the dioxin-like PCBs.[272] Given the additional known effects and accompanying uncertainties associated with the remaining PCB congeners, dual-track total PCB-based and TEF/TEQ-based assessments are recommended. More information is being generated and summarized for PCBs that are nondioxin-like.[273,274] Alternative methods for assessing these congeners in functional groups, as is being done for those that act through the Ah receptor, may be forthcoming and may be proposed for consensus adoption.

The primary consideration regarding the nondioxin-like congeners is the need to establish ecological relevance. For this, environmental exposure–effect relationships must be documented. The effects must be demonstrated in a toxicological significance range in which the exposure–effect is equal to or greater than for the dioxin-like congeners in the same species/life stage being assessed. More work with various animal classes will determine whether nondioxin-like congeners are as toxicologically significant as those that are dioxin-like. Invertebrates appear particularly attractive to study because they lack the Ah receptor. Aquatic organisms (fish, amphibians, and reptiles), in particular, require comparative study.

18.6.3 Effects Categories

Usually, the earliest sign of general toxicity from exposure to PCBs or PCDDs/PCDFs in controlled laboratory studies is weight loss. Female animals are more sensitive than males, and young animals are more sensitive than adults. Poultry, guinea pigs, mink, and nonhuman primates are the most sensitive.[275–277] Weight loss in chickens — "chicken edema disease" — is accompanied by increased bloating, which is actually an extracellular accumulation of body fluids and not real weight gain.[278,279] Terminally, rodents, mink, and especially birds show hemorrhage in the gastrointestinal tract.

18.6.3.1 Acute Signs of Poisoning

Acute signs of poisoning that are common include binding to the nuclear Ah receptor and resulting MFO induction of AHH and EROD. Following initial binding, induction or inhibition of other MFOs as well as hormonal and vitamin alterations can occur. Pathologically, subcutaneous, pericardial, and peritoneal edema, eyelid edema, hemorrhage, weight loss or reduced weight gain (termed "wasting" when accompanied by mortality), immune suppression, fatty infiltration of the

liver, hepatomegaly, and thymic (lymphoid) and gonadal atrophy have been demonstrated in numerous test species. All of the planar congeners show a degree of toxicity that relates to both the number and the locations of the halogen atoms. Lesser amounts of all of these planar compounds are needed to cause toxicity as the length of exposure increases. As an example, the single oral LD_{50} for 2,3,7,8-TCDD in monkeys was found to be 50 μg/kg, but if 500 ng/kg was administered over 6 months, then the cumulative LD_{50} was 2 μg/kg. Of the polychlorinated dioxins, 2,3,7,8-TCDD is the most studied because of its extreme toxicity to many organisms. Species information reveals the following rank order for adult LD_{50} TCDD sensitivity: guinea pig 1 μg/kg;[275] mink 4.2 μg/kg;[280] rabbit 115 μg/kg; chicken 25–50 μg/kg;[278] male and female rat 22 μg/kg and 45 μg/kg, respectively;[275] mouse 114 μg/kg;[281] bullfrog > 500;[282] and hamster 5000 μg/kg.[283] Comparably, Aulerich and associates reported interperitoneally injected newborn mink mortalities of 62 to 100% with a 1 ng/g TCDD daily dose for 12 days, and a dietary 135-day LC_{50} for mink of 0.05 μg/g for PCB 169.[284,285]

18.6.3.2 Chronic Signs of Poisoning

Chronic signs of poisoning in laboratory species include ligand binding, MFO induction, and other biochemical alterations, immunotoxicity, developmental defects, chloracne, cancer, and death.[286,287] Reviews by various authors indicate that the dioxin-like congeners correlatively manifest similar effects in a given species when dosages are adjusted to compensate for their lesser potencies relative to 2,3,7,8-TCDD. Interspecies sensitivity is variable, and not all acute and chronic symptoms of poisoning occur in every species. It is also very clear from the literature that life-stage sensitivity is exceedingly important in the full assessment of the effects of these compounds. For instance, the embryonic LD_{50} of 140 pg/g for TCDD in the chicken egg is 140–280 times higher than the LD_{50} in the adult.[278,288] For virtually all species tested, reproductive, developmental, and endocrine-related effects are the most sensitive endpoint indicators.

18.6.3.3 Endocrine and Mixed-Function Oxidase Effects

Available information suggests that dioxin-like exposures have the potential to compromise basic reproductive and developmental processes that can impair a population through modifying embryonic set points that are normally programmed for future survival and recruitment. The most responsive adverse effects are on the developing immune, nervous, and reproductive systems. In mammals, these effects have been observed at maternal body burdens of 2,3,7,8-TCDD in the range 30–80 pg/g for both nonhuman primates and rodents. While there is a 5000-fold acute adult lethality difference among guinea pigs, rats, mice, and hamsters, the doses associated with fetotoxicity are similar.[287] Among the most striking results of recent ecotoxicological relevant are those involving rats. Prenatal TCDD exposure toward the end of organogenesis produces permanent adverse effects in both male and female rat pups. Males exhibit delayed puberty, altered mating behavior, and decreased spermatogenesis, while females have a unique genital malformation that is characterized by a vaginal thread and cleft phallus, as well as premature reproductive senescence.[289–295] These effects occur at an estimated body burden of 28 pg/g over the background body burden of 4 pg/g of TCDD typically measured in rats and mice.[271]

There is a general relationship between the amount and timing of the dose for these compounds, not unlike "timing windows" for hormones. Lower dosage levels applied over longer periods of time can result in an identical toxic response of a single high dose. Developing embryos and early-life-stage compromise of basic maturation processes are known targets of these compounds. In this context, therefore, these endocrine effects can threaten maintenance of healthy ecological communities by compromising the ability of individuals to survive, breed, and recruit in a population. Because many of these congeners are persistent in the environment and magnify into higher trophic-level biota, full life-cycle exposures in laboratory testing are important for analyses of population effects.

Other noncancer endpoints have been researched and appear associated with endocrine disruption; these have been recently summarized by Birnbaum and Tuomisto.[287] Those with potential ecotoxicological significance that have been found in laboratory species exposed to TCDD and related compounds include: alterations of Leydig cells and normal dentition; induction of cleft palate and hydronephrosis; permanent lowering of core body temperature; onset of hearing deficits associated with circulating T4; learning deficits and impairments possibly associated with brain damage; locomotor and rearing behavior changes; promotion of endometriosis; thymic atrophy and decreases in thymic cellularity and depletion of all four subsets of T-cells; splenic atrophy; thyroid follicular cell hyperplasia; and changes in levels of androgens, estradiol, leutinizing hormone (LH), follicle stimulating hormone (FSH), vitamin A, thyroxine (T4), melatonin, insulin, glucose, serum gastrin, and glucocorticoids. Tissue-specific alterations of several glucocorticoid and estrogen receptor levels have been reported for doses as low as 0.1 of LD_{50}s. Alteration of nuclear retinoid receptor expression has been suggested as well as expression of mitogenic growth factors, such as epidermal growth factor (EGF). Many of these effects appear as direct or indirect divergences from hormonal homeostasis.

The most common sublethal biological effect of PCBs, PCDDs, and PCDFs across all vertebrate classes is increased activity in the hepatic microsomal MFO system. Many enzymes are induced or inhibited by exposures either *in vitro* or in the whole organisms. Typical environmental concentrations of TCDD and TCDD-equivalent tissue concentrations are less than 1.0 ng/g. Therefore, most typical effects on organisms will be through sublethal and chronic effects, as adult LD_{50} and LC_{50} values for the species known to be most sensitive are seldom approached in the environment, except at waste sites and in accidental poisoning episodes.

Physiological functions that are controlled by steroid hormones may be altered by exposure of organisms to PCBs, PCDDs, and PCDFs. Growth, molting, and reproduction are primary functions that can be affected by exposure of aquatic organisms to PCBs in numerous laboratory investigations. The ability of organisms to eliminate foreign organic compounds or endogenous waste products also may be affected. Steroid biosynthesis and the degradation and biotransformation of foreign compounds are metabolic activities in both fish and higher vertebrates that are strongly influenced by terminal oxidase activities of the microsomal cytochrome P450 system (or MFO system). Some, though not all, PCB congeners are MFO inducers in fish, mammals, and birds and to a lesser extent in aquatic invertebrates. There are excellent historical reviews on this topic, covering mammals, birds, and, more recently, fish.[265,276,277,296,297,299–301]

PCB metabolites can be more toxic than the parent compound.[261] Similarly, some steroids associated with reproduction may be oxidized or altered as a result of the metabolic process used by organisms in the attempt to depurate PCBs and PCDD/PCDFs.[302–304] Effects on reproduction in fish may occur prior to spawning, at spawning and egg deposition, or during egg and larval development. Steroid alteration can effect oogenesis, and the production of toxic metabolites can influence oocyte maturation.[304] Again, the difficulties in isolating these effects in the environment are severely compounded by the fact that they are very likely indirect, complicated by the interaction with nonchemically related environmental variables that also contribute to these responses. Some examples include deficiency syndromes associated with thiamine, vitamin D, or iodine that may be independent of, or interactive with, toxic effects from these compounds.[305–307] The increased sensitivity of organisms to PCBs, PCDDs, and PCDFs when challenged with exposure-independent and exposure-dependent deficiencies needs further elucidation.

18.6.4 Wildlife

Generally, the research to date on the effects of the mixed PCBs on mammalian wildlife agree with the data found for traditional laboratory animals. This is partly because few in-depth studies have been carried out on nontraditional laboratory animals, and thus our understanding is far from complete, especially with regard to full-life-cycle testing. For other nonmammalian species, several different types of responses have been observed.

18.6.4.1 Fish

18.6.4.1.1 Acute Effects of Poisoning

Laboratory studies indicate that fish vary in their acute response to PCBs. Eisler,[64] summarizing the LC_{50} responses of fishes, showed quite a considerable range depending on the Aroclor type, the species, and whether the species was marine or freshwater. The general level that produced lethality was in the 10- to 300-µg/g range (the exceptions were two marine fish that tested at 0.1 to 0.9 for long-term lab studies of 12 to 38 days). The longer the exposure period, the lower the LC_{50} value needed to kill the fish species. Early research found PCB toxicities in the range of 8 to 234 µg/L in various fish for 96-hour LC_{50} tests.[308,309] Trout species were found to require 1 to 62 mg/L to show LC_{50} values in 96-hour tests.[310]

In fish, the general characteristic of TCDD-induced toxicity is similar to that observed for mammalian species, i.e., there is a slow wasting-away syndrome leading to mortality. Furthermore, other symptoms are similar, i.e., reproductive toxicity, histopathologic alterations, and possibly immunosuppression and induction of cytochrome-P450-dependent monooxygenases.[256] Generally, concentrations causing observable effects were as follows: for rainbow trout, concentrations as low as 0.038 ng/L in flow-through systems caused mortality,[256] and adult carp (*Cyprinus carpio*) showed mortality after 71 days on 0.06 ng/L in the same study. Exposure of eggs caused the most dramatic effects: some residues as low as 40 pg/g in eggs caused mortality in lake trout (*Salvelinus namaycush*).[312] Other species were not as sensitive, e.g., rainbow trout exhibited mortality at 230 to 488 pg/g.[313] Later stages of growth were also less sensitive. Intraperitoneal injections of juveniles caused 80-day LD_{50}s at 5 ng/g in bullheads[314] and 3 ng/g in carp, whereas 16 ng/g of an intraperitoneal dose was required to produce mortality in bluegills (*Lepomis macrochirus*), and 11 ng/g were required in largemouth bass (*Micropterus salmoides*).

18.6.4.1.2 Chronic Effects of Poisoning

For PCBs, long-term toxicity tests on fish indicated little or no effect, even when high water concentrations or dietary exposures were tested. Salmon fingerlings fed 480 mg/kg Aroclor 1254 died after 260 days, while no effect was observed when catfish where fed 2.4–24 mg/kg of four Aroclors for 193 days.[310] Similarly, adult catfish fed 20 mg/kg Aroclor 1242 for 196 days showed no effect.[315] Day-old fathead minnows exposed to 0.9 to 5 µg/L Aroclor 1242 and 0.2 to 5 µg/L of Aroclor 1254 for 260 days showed no effects.[309] However, 10% lower growth of trout was observed when 17-day-old trout were exposed to 0.2 to 2.9 µg/L Aroclors 1254:1260 (1:2) for 90 days.[311]

Oviparous fish appear to show a wide range of reproductive sensitivities. Cold-water species such as lake trout, brook trout, and rainbow trout (*Onchorrhynhus mykiss*) are more sensitive than certain cool-/warm-water species, specifically the fathead minnow (*Pimephales promelas*), channel catfish (*Ictalurus punctatus*), lake herring (*Coregonus artedii*), Japanese medaka (*Oryzias latipes*), white sucker (*Catastomus commersoni*), Northern pike (*Esox lucius*), and zebrafish (*Danio rerio*).[316] The lake trout is the most sensitive (LC_{50} 65 pg/g_{egg}), while the least sensitive is the zebrafish (LC_{50} 2610 pg/g_{egg}). Thus, tested cool-/warm-water species are 8- to 38-fold less sensitive than lake trout. At the present time, hatching and early-life-stage studies have not been extended to partial and full life-cycle testing, which prolongs exposure, determines long-term survival, and looks for additional functional problems demonstrated in other animal classes. Much like the *in utero* effects in mammals, *in ovo* TCDD exposures in fish result in facial/jaw deformities, blue sac disease (yolk sac and pericardial edema), cranial edema, subcutaneous hemorrhaging, spinal deformities, and MFO induction — developmental symptoms similar to those seen in birds. The species differences in sensitivity may be due to variations in the length of time needed for fry to reach swim-up stage and fill their air bladders, in Ah-receptor toxicodynamics, and in toxicokinetics. Readers are urged to consult the underlying references in the WHO TEF scheme;[257] these references constitute the

basis for our understanding of the similarity of chronic effects of related congeners. They also document the diminished potency of the PCBs needed to produce these effects in fish relative to mammals and birds.

Toxicologically, it is important to consider the absorption/absorptive exposure in fish, rather than relying on water exposures. In a series of studies with the brook trout with natural accumulation of TCDD via contaminated food pellets, an adult whole-body concentration of 300 pg/g was sufficient to achieve egg concentrations associated with significant adverse effects on embryo survival and delay in time to initial spawning, suggesting that ovulation was affected. In a high-dose (1200 pg/g) treatment, the hepatosomatic index increases were dose-dependent in both sexes.[318] Companion study results[319] produced an LC_{50egg} of 138 pg/g wet weight at swim-up stage. Eggs constituted 39% of the adult whole-body concentration. Exophthalmia, cranial deformities, and generalized edema and hemorrhaging were observed, consistent with previous egg-injection studies in salmonids. Results from natural deposition of TCDD into the eggs resulted in a lower LC_{50egg} of 138 pg/g, compared to injection concentration of 200 pg/g in a previous study.[319] Threshold LC_{10egg} and LC_{90egg} values were 88 and 184 pg/g.

A physiologically based toxicokinetic model was also produced in the third paper of this series.[320] While affected individuals have not been raised to adulthood, it would obviously be beneficial to have observed these effects in older individuals. This is especially crucial for comparative purposes when wild fish observations are documented. For instance, striped bass (*Morone saxatilis*) have been characterized as having morphological abnormalities. Upon retrospective review of this study, these abnormalities qualitatively resemble certain dioxin-like induced effects (pugheadedness and skeletal) seen in the lower Hudson River and along coastal Long Island in New York during the mid-1970s.[321] Similar symptoms of bone-development abnormalities were seen in brook trout tested with Aroclor 1254; in these, backbone phosphorus and hydroxyproline as well as fry survival were reduced, and calcium backbone levels were increased, at fry whole-body concentrations ranging from 17 to 284 μg/g.[322]

Integration of abiotic and biotic exposure compartments is needed to address risk and to remediate excessive environmental pollution with these compounds. In a modeling paper discussing retrospective analysis of dioxin-like compounds using biota sediment accumulation factors (BSAFs) and dated sediment cores, lake trout from Lake Ontario were assessed. Effects on reproductive impairment were based on egg TEFs and toxicity equivalence concentration (TECs), defined as the sum of the products of the TEFs and the concentration of each congener in a mixture. In this case study based on egg TECs, lake trout suffered some early-life-stage mortality from approximately 1940 to 1990; for three of these five decades, they suffered total mortality. Eggs were contaminated by multiple dioxin-like congeners, with TCDD and PCB 126 exerting the predominant effects. Ecoepidemiological information confirmed this relationship through monitoring of feral, contaminated eggs under laboratory conditions and the appearance of naturally produced 1- to 2-year-old fish in 1994 when the level of the contaminants had declined.[323]

Atlantic salmon have been tested with a complex mixture of Aroclors 1016, 1221, 1254, and 1260. Tissue concentrations that were 5.6 μg/g from the 48-hour water exposure to this mixture produced reduced wet weight and length after 6 months. A higher tissue concentration (14.2 μg/g) was accompanied by altered behavior and reduced predation behavior by the fish.[324]

18.6.4.1.3 Endocrine and Mixed-Function Oxidase Effects

Endocrine and MFO effects of exposures have been investigated for several decades in fish, but with less firm results than for other animal classes. In early investigations, only thyroid effects were observed at very high-dose (0.4 to 650 mg/kg) Aroclor diets.[310] MFO activity in fish, however, is a major site of response to PCB exposure. Although increased activity of this system alone does not represent a toxicological threat,[325-327] it could have some negative aspects through the formation

and function of secondary products and downstream cascade effects from Ah-receptor binding. Thus, reexamination of old data may be warranted.

Reproductive toxicities have been documented in certain species of fish. Baltic flounder (*Platichthys flesus*) exhibited toxicity when ovary concentrations exceeded 0.12 mg/kg fresh weight.[309] Eisler cites several examples in his review chapter on PCBs:[64] among these, rainbow trout at 0.4 mg/kg Aroclor 1242 produced eggs with low survival and numerous fry deformities, rainbow trout at 0.33 mg/kg 1254 had 10 to 28% mortality, and Atlantic salmon at 0.6 to 1.9 mg/kg had 46 to 100% mortality. However, other studies on trout indicated that eggs with residue levels of 1.6 mg/kg did not have diminished survival.[317] Eggs exposed to water with 0.4 to 13 μg/L Aroclor 1254 had 21 to 100% fry mortality.[322] Thyroid hyperplasia has been observed in Great Lakes salmonids, and some attention has been given to this response in laboratory testing with PCBs. However, other than higher thyroid activity, no harmful effects have yet to be documented.[303,309,310]

2,3,4,7,8-pentachlorodibenzofuran, TCDD, and 2,3,7,8-tetrachlorodibenzofuran as well as ß-naphthoflavone inhibited vitellogenin synthesis in 17ß-estradiol-treated rainbow trout liver cells.[331] Potency of inhibition was directly related to strength as an inducer of CYP1A1 protein. PCB congeners 77, 126, and 156 did not inhibit vitellogenin synthesis and induced no levels or only moderate levels of CYP1A1 protein or EROD activity at molar concentrations that did produce vitellogenin effects from the tested furans and dioxin.

The pineal hormone melatonin, an important regulator of endocrine function and circadian rhythms in vertebrates, was investigated in rainbow trout primary hepatocytes. Treatment with 2,3,7,8-TCDD increased the major oxidative metabolite, 6-hydroxymelatonin, about 2.5-fold after 24 h and 1.2-fold after 48 h exposure, relative to the control cultures.[332]

Schmitt and co-workers[333] provided a description of the complexity of relationships in the environment for fish exposures to multiple contaminants, including PCBs, PCDDs, and PCDFs from various regions of the United States, specifically the Mississippi, Columbia, and Rio Grande River watersheds. The yolk protein, vitellogenin, occurrence in plasma and ovarian cells in the testes of male fish from several sites, along with abnormal ratios of sex steroids, suggesting that fish from some sites are exposed to endocrine-modulating substances. Because of the antiestrogenic activity of dioxin-like PCBs, PCDDs, and PCDFs, it is difficult for these compounds to be clearly implicated in male fish vitellogenin induction (a hallmark of an estrogenic substance). However, the abnormal sex steroid ratios might be implicated. Hydroxylated PCBs, which are not dioxin-like, may be important in vitellogenin induction and feminization of male fish; they require further male-specific investigation.

Aroclor 1254 disrupted reproductive/endocrine function in Atlantic croaker (*Micropogonias undulatus*) when they were fed a dietary concentration of 0.5 mg/100g body weight for 17 days. Ovarian growth was impaired, and vitellogenesis decline was associated with a decline in plasma estradiol. *In vitro* spontaneous secretion of gonadotropin from pituitary glands of PCB-treated fish was also demonstrated.[334] More recent work in this species, again with exposure to Aroclor 1254 (dietary dose 1 μg/g for 30 days), demonstrated reduced serotonin, dopamine, testosterone and 11-ketotestosterone, testicular growth inhibition, and reduced testicular gonadal somatic index.[335,336]

Endocrine stress response and abnormal development were demonstrated in carp that were water-exposed to PCB 126.[337] At 10^{-10} and 10^{-11} mol L^{-1}, PCB 126 altered the levels of stress hormones, andrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (MSH), and cortisol in whole-body measurements. Swelling of the yolk sac and pericardium occurred, indicating that edema was induced, as well as PCB-stimulated body pigmentation thought to be mediated by elevated α-MSH at all PCB 126 test concentrations.

TCDD, PCB 126, β-napthoflavone, benzo(a)pyrene, and diindolylmethane caused a concentration-dependent suppression of the secretion of vitellogenin, which was related to the response observed with E2-treated cultured female carp hepatocytes. The order of potency for suppression of vitellogenin secretion was comparable to the order of potency for CYP1A induction. These

investigators suggested that the antiestrogenicity of these compounds, while AhR-mediated does not involve CYP1A. This could be relevant for feral fish populations, as they are frequently exposed to Ah-receptor agonists at levels at which AhR-mediated effects are observed.[338]

Study of multiple exposures exemplifies the difficulty in establishing cause-and-effect relationships without complementary laboratory and combined field/laboratory study designs. The joint toxicity of tributyl tin (TBT) and PCB in the diets of Japanese medaka demonstrated additive effects on spawning success but antagonistic effects on embryological success of eggs and swim-up success of larvae.[339]

In a study of zebrafish,[340] 17ß-estradiol; 2,3,3',4,4',5,6-HpCB (PCB-190); 2,3,4,4'-TeCB (PCB-60); and 2,2',4,6,6'-PeCB (PCB-104), which are PCBs considered to be nondioxin-like, increased embryo and larval mortality. The most severe effects on viability were observed following treatment with 17ß-estradiol or the weakly estrogenic PCB-104. Delayed embryo development and hatching were seen. PCB-190 showed only moderate effects on early-life-stage mortality. The fish were reared until sexual maturation, after which they were subjected to gross morphological and histological analyses. Changes in morphology were observed following PCB-104 and PCB-190 treatment. Both substances produced craniofacial malformations, while PCB-104 induced lordosis in females and scoliosis in fish of both sexes. From histological analysis it was found that PCB-104 and 17ß-estradiol resulted in karyorrhexis and karyolysis in the kidney. Ovaries showed atresia and limited failure of testicular spermatogenesis in fish treated with 17ß-estradiol, PCB-104, or PCB-60. This study demonstrated that xenoestrogenic substances are embryotoxic and manifest certain characteristic symptoms in common with the dioxin-like effects, although obviously through a different primary mechanism.

PCB 81 was tested in juvenile rainbow trout and was found to be 0.004-fold as potent as TCDD in the induction of AHH activity.[341] When investigated in medaka embryos in this study, PCB 81 was more toxic than PCB 77, and TEFs of 0.0014 and 0.006 were determined for mortality and for swim bladder inflation, respectively.

Detailed reviews that address PCBs and dioxins have recently covered the effects on the immune, MFO, and endocrine systems in fish.[301,342–346]

18.6.4.2 Birds

18.6.4.2.1 Acute Effects of Poisoning

As noted by Eisler,[64] birds are more resistant to acutely toxic effects of PCBs than are mammals. LD_{50}s ranged from the 60s to > 6000 mg/kg diet for several birds tested in laboratory studies.[62] Little field mortality can be ascribed to PCBs. In southern Ontario, high PCB exposure, as indicated by levels in the brain in excess of 310 µg/g, were believed to have caused mortality in ring-billed gulls in late summer and early autumn 1973.[347] This mortality may also have been caused by high PCDF and PCDD contamination, which is well documented in the Lake Ontario ecosystem.

Birds that forage within aquatic-based foodchains, such as gulls, terns, herons, and mergansers, can accumulate relatively high concentrations of PCBs and PCDD/PCDFs. They differ from true terrestrial species, such as passerine and gallinaceous birds, which generally have lower concentrations of PCBs and PCDD/PCDFs. However, for eagles, falcons, hawks, and owls, which are at the top of their respective food chains, there is a potential for high exposure due to their high biomagnification potentials (i.e., 10,000 and higher) and their unique feeding habits. Those individual species that possess feeding strategies in which they hunt other birds (or their eggs) and mammals — which already may be exposed and also have biomagnified these contaminants — will have the highest exposures and will possibly move past an effects threshold. Additionally, for birds that are scavenger feeders, e.g., foragers at municipal dumps or dead carcasses of seals, the potential for exposure is high, though dependent on the frequency of such behavior.

Laboratory Species — There are considerable data for PCB toxicity and more limited data for PCDD toxicity to chickens. This species appears to be unusually sensitive to PCBs and dioxin-like compounds in general. The term "chick edema disease" was first used during investigative studies of unintentional poisonings in young chickens (reviewed in Firestone[348]). Chick edema disease was caused by 1,2,3,7,8,9-HpCDD, which was discovered in chicken feed that was contaminated with a "toxic fat" food supplement. The toxic fat was linked to the degreasing of cattle hides with pentachlorophenol, the ultimate source. More interpretive PCB and PCDD studies have been conducted with chicken (*Gallus gallus*) than with any other bird species.

Pen and Laboratory Studies — Adult and juvenile birds of precocial species exhibit varying sensitivities to ingestion of Aroclor and PCB mixtures. In 5-day feeding trials, dietary median lethal concentrations (8-day μg/g-LC_{50}s) were 604 with Aroclor 1254 for northern bobwhite (*Colinus virginianus*), 1091 for ring-necked pheasants (*Phasianus colchicus*), 2697 for mallards (*Anas platyrhynchos*), and 2895 for Japanese quail (*Coturnix japonica*).[349] In a related publication on this same Aroclor toxicity study, Heath and co-workers[279] documented the complete absence of fat and the presence of pericardial edema in lethally poisoned bobwhite chicks — characteristics of chick edema disease. This early study also tested the joint lethality of Aroclor 1254 and p,p'-DDE to Japanese quail chicks, using three different but wide-ranging ratios; it found that all combinations "proved to be essentially additive" in the joint action of the two compounds. This has implications for causal determinations of reproductive impairment in the wild where multiple contaminant exposures are common and where statistical significance alone, on a chemical-by-chemical basis, may not account for combined causal associations that are biologically significant.

Dahlgren and co-workers[350] administered capsules daily containing 10, 20, or 210 mg of Aroclor 1254 to 11-week-old hen pheasants until death or sacrifice. PCB ingestion, at all levels in a dose-dependent fashion, killed birds, with those receiving the least PCB taking longer to die. The authors concluded that a brain residue level of 300 to 400 μg/g was indicative of death due to PCB toxicosis. Further studies by these authors[351] revealed that periodic food deprivation increased brain residues, leading to more rapid death.

Young cockerels (day-old at start) that died on dosage of 600 μg/g Aroclor 1260 contained 270 to 420 μg/g of PCBs in the brain.[352] Dosage with phenochlor and chlophen (60% chlorine mixtures) resulted in more variable residues, and these two formulations were more toxic than Aroclor 1260 and produced pathological signs. However, both of these formulations proved to be contaminated with chlorinated dibenzofurans.[353] Pathological examination of these chickens revealed severe edema and lesions.

Wildlife Species — Studies conducted with altricial species of birds have included observations with cormorants, herons, finches, and blackbirds. Great cormorants (*Phalacrocorax carbo*) dosed experimentally with clophen A 60 died with brain residues of 76–180 μg/g (mean, 130) whereas herons that died on clophen dosage contained 420–445 μg/g, suggesting that cormorants were more sensitive than herons.[354] These authors concluded that survival time in cormorants was related to the capacity of the birds to store the PCBs in adipose and other tissues, apart from brain, indicating that total-body content is not a good criterion by which to assess mortality.

As observed above, lethality in birds appears to be correlated with brain residue levels. Stickel and co-workers[355] conducted one of the most comprehensive studies designed to establish lethal brain residues of PCBs, using Aroclor 1254, in passerine species. These species included immature male common grackles (*Quiscalus quiscula*), immature female red-winged blackbirds (*Agelaius phoeniceus*), adult male brown-headed cowbirds (*Molothrus ater*), and immature female starlings (*Sturnus vulgaris*). PCB residues in brains of birds that died were distinctly higher than those in sacrificed survivors, providing suitable diagnostic criteria. PCB residues varied from 349 to 763 μg/g wet weight in brains of dead birds and from 54 to 301 μg/g in sacrificed birds. The authors considered a threshold of 310 μg/g to be diagnostic of PCB-induced mortality. PCBs in brains of

dead birds for three species did not differ significantly from one another, but residues in starlings (mean 439 μg/g) averaged significantly lower than for red-winged blackbirds and grackles.

18.6.4.2.2 Chronic Effects of Poisoning

Egg Injection Studies — Most chronic-effects studies have focused on the reproductive outcomes of embryonic exposure to PCBs and PCDD/PCDFs. Egg-injection studies have been successfully utilized to mimic natural deposition of these lipophilic contaminants from a laying hen, either by introduction into the air sac or direct yolk-sac injection. Additionally, several methods have been used to observe the reproductive effects of chronic adult exposure, including dietary, water, and injected exposures of the hen to the toxicant, as well as allowing for natural deposition into the egg, in which yolk is the toxicant reservoir. As in other experiments, it appears that (1) the longer the exposure, the greater the effect, and that (2) the earlier in development the compounds are administered (day-zero exposure in an egg), the greater the toxic effect. This makes it difficult to separate out general chronic toxicity from that mediated indirectly through endocrine system disruption. All of the above effects appear to be related for these (PCBs and PCDD/PCDF) compounds.

Laboratory Species — In a white leghorn study, hens received diets containing 0 to 80 μg/g Aroclor 1242 for 6 weeks.[356] Egg production, egg weight, shell thickness, and shell weight were not affected, but hatchability was affected within 2 weeks for hens fed as little as 20 μg/g dry weight. Yolks contained 2.4 μg/g (expected whole-egg concentration of 0.87 μg/g). This conversion is based on the chicken yolk comprising 0.364 of the whole-egg content mass.[357] Even 10 μg/g dry weight in the diet caused a small reduction in hatching at the end of 6 weeks (yolk concentration of 3.7 μg/g, or expected whole-egg concentration of 1.3 μg/g). Scott[358] reported that hatchability was decreased after 4 weeks of Aroclor 1248 at 10 μg/g dry weight in the diet, with egg residues of 22.7 μg/g.

Numerous egg-injection studies have been conducted with PCBs in the chicken egg. Blazak and Marcum[359] injected Aroclor 1242 into the air cell of fertile white leghorn eggs. Both 10 and 20 μg/g caused 64 to 67% mortality but did not result in chromosomal breakage, as had been reported in ringed-turtle doves by Peakall and co-workers.[360] Srebocan and co-workers[361] injected Aroclor 1254 into chicken egg air cells and noted decreased activity in key gluconeogenic enzymes. Brunstrom and Orberg[362] injected white leghorn eggs, after 4 days of incubation, into the yolk sacs to attain egg concentrations of 0, 1, 5, and 25 μg/g of Aroclor 1248. Hatchability was 96, 92, 17, and 0%, respectively, with mortality occurring the earliest in the 25 μg/g group (days 6–12). A great number of egg-injection studies have been conducted with specific PCB congeners studying the effects in chickens and other species. Rifkind and co-workers[363] injected chicken eggs at 10 days of incubation with 5 to 1000 nmol/egg for each of three PCB congeners (77, 169, and 2,2',3,3',6,',6'-HCB (PCB 136). PCB 77 caused dose-related decreases in survival from day 10 through 19 days of exposure at 100 to 1000 nmol/egg, and PCB 169 at 500 to 1000 nmol/egg. These decreases in survival were accompanied by decreased thymus weight and increased pericardial and subcutaneous edema in surviving embryos. Another study by these authors revealed that hepatocyte swelling, the major histopathologic change, was apparent within 24 h, after doses as low as 5 nmol/egg for PCB 77.

Wildlife Species — Effects of PCB congeners 126 and 77 in chickens, common terns (*Sterna hirundo*), and American kestrels (*Falco sparverius*) were studied through hatching, following air-cell injections on day 4 of incubation.[364] In the chicken, kestrel, and common tern, the LD_{50}s for PCB 126 were, respectively, ~0.4 ng/g_{egg}, 65 ng/g_{egg}, and 104 ng/g_{egg}. This study also demonstrated that PCB 77 was about fivefold less toxic than PCB 126 in the chicken model (LD_{50} 2.6 ng/g_{egg}). In the kestrel, the LD_{50} for PCB 77 was 316 ng/g_{egg}. In common terns, deformities occurred at egg concentrations at which hatching success was affected, whereas malformations occurred below those concentrations affecting hatching success in the chicken and kestrel. Hatching success,

malformations, and edema in this study were consistent with the reproductive problems identified in other recent laboratory studies of chickens[288,365] as well as Great Lakes species (Forster's tern, common tern, Caspian tern, double-crested cormorant, bald eagle, and herring gull).[366-369]

Probably the most important finding of the study was on kestrels, considered as a surrogate species for interpreting effects on the bald eagle in the Great Lakes and elsewhere. Eagle eggs from New Jersey[370] and the Great Lakes,[371,372] areas where reproductive impairment including malformations[373] have been documented, contained elevated PCB 126 concentrations at 2–4 ng/g egg to 42 ng/g egg fresh wet weight. PCB 126 is always the largest contributor to TCDD TEQs in birds having significant PCB exposure. In kestrels, malformations begin occurring at 0.23 ng/g_{egg}, combined malformations and edema are statistically different from controls at 2.3 ng/g_{egg}, and malformations alone are statistically different at 23 ng/g_{egg}. These findings present a plausible explanation for the occurrence of bill defects in Great Lakes eaglet nestlings. Growth retardation indicators of toxicity measured in exposed kestrels (hatch weight, liver weight, and femur length) were statistically significant at 0.23 ng/g_{egg}. Although these effects have not been studied directly in bald eagles because of their protected status, it seems reasonable to expect growth retardation in more highly exposed individual hatchlings, leading to reduced productivity and reduced survival from other chronic stressors. Kestrel chick developmental toxicity was shown to be lower than for embryos and higher than for adults.[374]

In an exposure study using carp from Saginaw Bay, Lake Huron as a weathered, environmentally relevant source, white leghorn hens were administered between 0.3 (control (0%) carp) and 6.6 (high-dose [35%] carp) mg/kg/day total PCBs, yielding time- and dose-dependent reproductive toxicity.[375] Embryos displayed typical embryo mortality and reduced hatchability, as well as classic deformities including head, neck, and abdominal edema, hemorrhaging, and foot, leg, skull, brain, and yolk-sac deformities. Organ weights were significantly affected including livers, spleens, and bursas. Hatched chicks showed significant effects on body, brain, liver, heart, and bursa weights. These effects are all consistent with the establishment of Koch's fifth postulate, which requires the hypothesized putative factor to be introduced into the test organism and to reproduce symptomatic adverse effects. In this case, the sensitive model species was utilized as a surrogate for fish-eating birds that have demonstrated historical symptoms of PCB and dioxin-like reproductive toxicity.[366-368]

Comparative avian egg-injection studies by Brunstrom and co-workers have shown that chickens are more sensitive than turkeys (*Meleagris gallopavo*), pheasants, ducks (mallards and goldeneyes (*Bucephala clangula*), domestic geese (*Anser anser*), herring gulls, and black-headed gulls (*Larus ridibundus*).[376]

Reproductive impairment has been reported in at least five species of birds that were experimentally dosed with PCBs including chickens, ringed-turtle doves (*Streptopelia risoria*), Japanese quail, mourning doves (*Zenaida macroura*), and ring-necked pheasants. Egg production was reduced with 5 μg/g in the diet, but hatchability was unaffected. However, after 14 weeks, fertility was lower. Hatchability of fertile eggs was only affected when the PCB concentration exceeded 15 μg/g in eggs; at such levels, embryonic mortality was high and occurred at earlier stages. In contrast, Cecil and co-workers[377] reported that dietary levels of 20 μg/g for Aroclor 1254 did not affect hatching success of chickens at the end of 5 weeks with egg residues of 13.2 μg/g. Tumasonis and co-workers[378] exposed white leghorn hens for 6 weeks to 50 mg/L Aroclor 1254 in drinking water. Within 2 weeks, hatching success dropped to 34%. The authors concluded that yolk concentrations > 10–15 μg/g (whole egg concentrations above 4 μg/g) were required to cause this effect. Peakall and Peakall[379] found that 10 μg/g of Aroclor 1254 caused increases in embryonic mortality of ringed-turtle doves; this effect was greatly increased when the eggs were incubated by the parents, but it was decreased by artificial incubation. Monitoring of egg temperatures suggested that mortality increased with decreased parental attentiveness. Further studies with Aroclor 1254 in this species revealed depletions of brain dopamine and norepinephrine that were inversely correlated with brain residues.[380] Other species appear to be less reproductively sensitive to PCB exposure.

Neither Aroclor 1254 nor Aroclor 1242 affected reproductive success of mallards. Other tests showed screech owls (*Otus asio*) and Atlantic puffins (*Fratercula arctica*) to be unresponsive.

In a more recent iteration of the determination of relative species sensitivity to PCB 126,[365] a comparative investigation of yolk-sac-injected eggs demonstrated marked differences in relative embryo mortality sensitivity in the following rank order (most sensitive to least): white leghorn, turkey, common tern, and Japanese quail. For the common tern, the results are consistent with findings by Hoffman and co-workers,[364] although the two studies used different dosage methods. The bobwhite is much more sensitive to PCB 126, based on the reported LD_{50} of 24 ng/g_{egg},[364] than is the Japanese quail, with a no-effect concentration on mortality of 240 ng/g_{egg}.[365] For the former, the divergence is consistent with early feeding studies of these species in which bobwhites were three to four times more sensitive in dietary acute exposures with various Aroclors.[279] In contrast, the piscivorous double-crested cormorant is intermediate in sensitivity, with an LD_{50egg} for PCB 126 of 158 ng/g.[381]

Among the various bird species that have been tested with 2,3,7,8-TCDD, the ring-necked pheasant was the most sensitive besides the chicken, with egg injections of 2.1 ng/g producing $LD_{50's}$ and 25 ng/g i.p. for 80% mortality in the adult hen after 77 days. Other studies[382] with ring-necked pheasant determined that the delayed onset of mortality occurred at a single injection of 25 µg/kg. With repeated injections, the cumulative level of 10 µg/kg over 10 weeks caused similar symptoms. Egg-injection studies of ring-necked pheasant eggs demonstrated LD_{50}s of 1.35 and 2.2 pg/g, respectively, for albumen and yolk injections..[383] Bobwhite were sensitive to an LD_{50} dose of 15 ng/g in their feed,[384] but mallards and ringed-turtle doves showed no response at concentrations greater than 108 and 810 ng/g of feed (single dose), respectively.

Among the most compelling case histories available to document the reproductive problems caused by PCBs is for Green Bay Forster's terns (*Sterna fosteri*) in the 1980s. Egg-intrinsic and adult behavioral nest-attentiveness problems lead to a variety of measurement endpoints, including wasting syndrome, as documented in a followup[385] to the original study, and provide convincing ecoepidemiological evidence for total PCBs as well as TCDD equivalents as the putative causative factors, as measured in study eggs.[386-390] The above findings did not determine DDT/DDE to be important to Forster's tern reproductive impairment. Additional work on this species, subsequently conducted in Texas, showed that total PCB egg residues were low and that DDT/DDE residues were greater than those at Green Bay; however, reproductive success was normal.[391] This study represents an independent confirmation of the importance of the PCBs in Green Bay, conducted by other investigators in a different time and ecosystem.

Wasting syndrome has been documented to various degrees in fish-eating colonial waterbirds, in at least three Great Lakes species investigations, for Forster's terns,[385] Caspian terns,[392] and herring gulls.[393] A comprehensive review by Hoffman and co-workers[368] should be consulted for historical toxicity information from both the laboratory and field study of birds with these compounds.

18.6.4.2.3 Endocrine and Mixed-Function Oxidase Effects

Histological and Biochemical — Comparison of the toxicities of PCB congeners injected into the yolk sac of chicken eggs at an early stage of development (4 days of incubation) revealed that PCB 126 was the most toxic and also the most potent inducer of MFO (EROD) in chick embryo liver.[394] The EROD-inducing potencies correlated well with the embryolethalities. When injections were administered at the earlier stage of incubation (day 4) via the yolk sac and eggs were incubated until day 18, the congeners were even more toxic. Non*ortho* chlorinated congeners were more potent inhibitors than were *mono-ortho*-chlorinated congeners of lymphoid development in the embryonic bursa of *Fabricius*.[395] The most immunotoxic of the *mono-ortho*-chlorinated analogs of PCB 77 and PCB 126 were about 1000 times less potent than PCB 126.

18.6.4.2.4 Other Effects

Specific congeners have been tested as inducers of porphyria in Japanese quail and American kestrels.[396,397] Liver residue levels for PCB 105 of 2.6 ± 1.7 mg/kg, and for PCB 126 of only 0.091 ±0.08 mg/kg were found to cause porphyria after 2 weeks in Japanese quail.[398] PCB 153 at 52.6 mg/kg in the liver had minimal effects. PCB 126 caused a decrease in thymus weight. All three congeners induced MFO activity as detected by the EROD assay. In American kestrels, residue levels in pooled adipose tissue of 182 mg/kg for PCB 105, of 119 mg/kg for PCB 153, and of 3.3 µg/kg for PCB 126 did not cause porphyria but did induce hepatic MFO activities.[397]

Studies have examined the effects of specific PCB congeners on growth. The effects of feeding 400 µg/g of five hexachlorobiphenyl congeners, including 2,2',4,4',6,6'-HCB (PCB 155), 2,2',3,3',6,6'-HCB (PCB 136), 2,2',4,4',5,5'-HCB (PCB 153), 2,2',3,3',4,4'-HCB (PCB 128), and 3,3',4,4',5,5'-HCB (PCB 169), were examined in growing chicks for 21 days.[398] PCB 169 was the most toxic, causing complete mortality, and it produced the highest accumulation (mean of 203 µg/g) of all congeners in the liver. Growth was reduced by all congeners except PCB 155. Liver-to-body weight ratio was increased by all congeners, with the largest increase produced by PCB 155 and the smallest by PCB 136. Another study examined the effects of PCB congeners 126, 77, and 105 on growth and development of American kestrel nestlings.[374] Dosing with 50 ng/g resulted in pronounced liver enlargement and some mild coagulative necrosis of the liver. Increasing the dose to 250 ng/g resulted in intensification of the above effects as well as lesions of the thyroid, decreased spleen weight, and lymphoid depletion of the spleen and bursa.

In testing of PCB 126 in primary immune organ development,[399] thymus mass decreased at doses between 0.13 and 0.32 ng/g_{egg} and thymic lymphoid cell numbers dropped sharply at doses between 0.051 and 0.13 ng/g_{egg} when injected into chicken egg air cells. Similarly, bursa mass began to decrease at the lowest dose (0.051ng/g_{egg}). The number of viable cells decreased across the dose range and reached a minimum at 0.13 ng/g_{egg}. The study concluded that (1) lymphoid cell numbers were more sensitive than organ mass, (2) bursa was more sensitive than the thymus, and (3) the doses to reduce the quantity of viable cells were at least an order of magnitude lower with full-term embryo exposure (day 0–7 injection before incubation, and day-20 egg opening, in a normal 21-day incubation) than with late-stage exposure only. In a related study,[400] thymocyte phenotype TCR-ß$^+$ decreased with dose as a function of the declines in TCR-ß$^+$ percentages and total thymocyte numbers. The number of viable lymphoid cells in the bursa decreased to 45% lower than in controls at 0.13 ng/g_{egg} and fell to 76% lower than the controls at 0.8 ng/g_{egg}. The authors also calculated that these immunological effects were comparable to those found in Great Lakes herring gull eggs, after correction for interspecies differences in sensitivity to PCB 126. Other related studies on Saginaw Bay Caspian terns have suggested a biologically significant effect on immune function by PHA (phytohemagglutinin), which measures T lymphocyte response.[401] PCB concentrations correlated with reduced immune function to a greater extent than did those of DDE, although both types of compounds were significantly correlated in plasma and eggs. These authors also observed that these and other immune-function tests[393,402] suggest an association with the reduced recruitment of young terns into the contaminated Saginaw Bay ecosystem that has been characterized through studies of breeding reproduction and population dynamics.[403]

Environmental Extract Egg-Injection Studies and Vitamin D — In another approach to understanding relative sensitivity, extracts obtained from Great Lakes double-crested cormorants were injected into chicken eggs. One egg-equivalent of cormorant extract injected into chicken eggs produced 77% embryo mortality.[404] Yet at these levels, no malformations occurred, which is unusual, whereas body weight and relative bursa weights were reduced, while relative brain weights were increased.

Egg-injection studies with extracts from wild bird eggs have failed to produce statistically significant increases in deformities in cormorants,[381] chickens,[404] or herring gulls,[405] suggesting that

another factor or factors (such as vitamin D deficiency[306]) may be altered during egg development and that this cannot be duplicated in "clean" test eggs. One possibility that has received little attention in ecotoxicological or laboratory studies is that PCBs may alter deposition, in either form or amount, of vitamin D in egg yolks. Vitamin D is lipid-soluble and is critical to proper bone development. Vitamin D is twice hydroxylated, once by hepatic 25-hydroxylase and a second time by renal hydroxylase, to produce the hormone-like activity of 1α,25-dihydroxycholecalciferol that is used for calcium regulation and bone deposition. Additionally in the Great Lakes, where bill defects in cormorant nestlings[406] and dead embryos[407] are relatively common, altered vitamin D deposition into the yolk could be influenced by exposure of cormorant hens to dioxin-like congeners prior to egg laying. This could be a cofactor in the incidence and prevalence of bill defects, along with dioxin-like congener exposure *in ovo*. Under the combined influence of altered enzyme activity and *in ovo* dioxin-like congener contamination, there could be a deficiency, excess, or altered availability of 1α,25-dihydroxycholecalciferol that could be related to bill and skeletal defects or even embryonic mortality.[408]

Embryonic exposure, together with effects in the environment, could result in an enhanced sensitivity of embryos that are simultaneously deficient in available vitamin D and that have altered egg proteins that are associated with reduced vitellogenin synthesis caused by antiestrogenic, dioxin-like congeners. Ascertaining whether such a relationship exists would help to resolve outstanding inconsistencies between extract-based egg injection studies and adult feeding protocols.[375] Investigations along these lines may also help explain the puzzling observation that cormorants exposed to low PCB levels developed bill malformations only after hatching and in conjunction with vitamin D-deficient diets (frozen fish) and sunlight deprivation (resulting from indoor zoological captivity).[306]

Several lines of evidence suggest that during embryonic development, vitamin D, calcium requirements, and vitellogenin formation can be linked to embryotoxic and teratogenic effects caused by certain dioxin-like compounds. Basic bird research on vitamin D has demonstrated that 1α,25-dihydroxycholecalciferol-deficient Japanese quail embryos die of calcium deficiency at day 15 of development when hens produce vitamin D-deficient eggs. Single doses of 125 ng cholecalciferol, 600 ng 24,25-dihydrocholecalciferol, or 100 ng 1α,25-dihydroxycholecalciferol increased hatchability when injected into eggs prior to incubation, but they were toxic when injected into eggs on days 11 and 12. *In vitro* formation of vitellogenin by liver slices of vitamin D-deficient hens is reduced to less than 30% of that occurring in vitamin D-sufficient controls, and vitamin D-deficient hens have lowered Ca2+ in blood plasma.[409] It is not known whether any yolk-related proteins or binding proteins are altered in vitamin D-deficient adult birds. In a review of the primary literature on comparative avian nutrition,[410] Klassing's discussion of vitamins A and D, among others, provides additional evidence for a potential relationship between embryotoxic and teratogenic effects that are consistent with certain dioxin-like effects. For instance, vitamin D-deficient embryos can develop deformed mandibles and beaks and problems pipping the shell due to overall weakness, and they can have poor bone calcification.

Summary Information — Besides the studies addressed above, recommended resources on the following selected topics are: MFO effects in birds,[300,411,412] and in-depth development and documentation on TEFs (www.who.nl).

18.6.4.3 Mammals

18.6.4.3.1 Acute Signs of Poisoning

The hallmark responses of MFO induction — wasting and edema — are common to most tested species. In addition, there are species-specific signs of acute toxicity that have been documented. In the monkey, alopecia and swollen eyelids have been demonstrated. In mink, lethargy, anorexia,

hemorrhaging, and hemorrhagic gastric ulcers are symptomatic, along with a dose-dependent decrease in feed consumption with corresponding body weight loss. Gross necropsy revealed mottling and discoloration of the liver, spleen, and kidneys. In mink that are exposed to high doses of TCDD, brain, kidneys, heart, and thyroid and adrenal glands all become enlarged relative to the organism's body weight.[280] Fatty infiltration of the liver may or may not occur, depending on the length of the acute exposure. In the European ferret, which is less sensitive than the mink, claws become markedly curled, with an appearance similar to deformed bills in birds.[413] Similarly, hooves of horses that curled upward was a documented effect observed in horses exposed to horse-arena soil that was contaminated by TCDD from a 2,4,5-T manufacturing facility. The episodic horse exposure is not common in the general environment, whereas acute exposures of mink to TCDD and dioxin-like chemicals in contaminated ecosystems are still possible.

18.6.4.3.2 Chronic Signs of Poisoning

General Indicators — Skin lesions are generally observed in various species. The specific class of compounds first ascribed to causing this response was the chlorinated naphthalenes that caused the hyperkeratotic disease of cattle in the United States labeled "X-disease." Later an "X-disease-like symptom" was associated with chlorinated dioxins and chlorinated dibenzofurans;[10] PBBs caused skin lesions like the X-disease in cattle in Michigan,[414] and Old World monkeys developed chloracne and a thickened condition of the eyelids.[415] McConnell[10] listed the following chronic features associated with poisoning by these agents. Chloracne-like lesions are not usually observed in rodents. Internal lesions are quite common with these classes of compounds; such lesions vary with duration of exposure and depend especially on the age of the organism being tested. In all experiments involving immature animals, the size and weight of the thymus are markedly less than in the controls. Chronic effects in blood are quite variable; however, the one common component observed in most long-term studies is a dose-time-related anemia that is postulated to be due to the toxic effects on erythropoiesis from all of these types of compounds. The carcinogenic potential of PCBs and dioxins has been studied, but information on dibenzofurans is not available. Dioxins, specifically TCDD and HxCDD, have been shown to be carcinogenic in rats and mice by several investigators. The reproductive effects from intoxication with PCBs and dioxins have been studied in depth.

The first reported reproductive dysfunction that was suggested to be a result of intoxication with the general class of compounds to which PCBs, dioxins, and dibenzofurans belong was observed in a study of women exposed during 1968 to PCBs in Yusho, Japan. These women exhibited irregularities in their menstrual cycles. As stated earlier, the likely components causing these problems were dibenzofurans and dioxin impurities in the PCBs. TCDD has been reported to affect the testes and accessory male reproductive organs. TCDD also adversely affects spermatogenesis and testosterone levels.[416] Many reports of TCDD developmental toxicity are available. TCDD causes cleft palate in mice and other manifestations of developmental toxicity in other species. Furans also induce cleft palate and hydronephrosis in responsive mice. Additional studies of the effects of TCDD on palate and kidney development have been reported. There are considerable differences in toxicity among members of the chemical classes that make up the dioxins and the furan series of compounds.

Metabolism and excretion are assumed to be important modes of detoxification of these chemicals. Exposure of target tissues is to a great extent closely related to chemical solubility and lipophilicity of the particular compounds. Solubility tends to decrease with increasing degree of halogenation, as do the extent and rate of metabolism (and therefore elimination). Thus, highly halogenated members of the groups tend to be more persistent and to have greater potential for bioaccumulation. Those halogenated dioxins, and furans with adjacent unsubstituted carbon atoms, are more readily metabolized than are those without this feature. The symmetrical tetrachlorinated dibenzo-*p*-dioxins and dibenzofurans have no adjacent unsubstituted carbon atoms and are the most toxic members of their respective classes, including developmental toxicity.

Regarding relative species and strain sensitivities, clear differences among species in susceptibility to developmental toxicity have been reported that are relatable to inherent genetic susceptibility, differences in tissue disposition of the chemical, and perhaps other factors that are currently not understood or appreciated. In general, adverse reproductive effects have been caused in multiple species by 2,3,7,8-substituted dioxins. Greater species differences are noted for developmental toxicity than for adverse reproductive effects. Mice are generally more likely to demonstrate malformations, with or without effects on size of pups or litters. In contrast, rats are more likely to have resorption or decreased fetal weight than malformations. Nonhuman primates are more likely to show an effect on fertility and *in utero* survival than abnormalities of structural development. Observations on humans exposed accidentally to dioxins suggest that humans are not more sensitive to adverse reproductive developmental effects than laboratory animals.[416] Additionally, the recent WHO reevaluation of the "tolerable daily intake" for humans estimated the body burdens of laboratory animals at their respective lowest observed adverse effect levels (LOAELs). Those body burdens were transformed into estimated daily human intakes that on a chronic basis would be expected to lead to similar body burdens in humans. The reevaluation noted that "the estimated human daily intakes are related to the body burdens in animals where adverse effects have been reported."[271]

Mink — Hochstein and co-workers[417] determined the LC_{50} dietary concentration in adult female mink fed TCDD for 28 or 125 days. Based on feed consumption of control mink, LC_{50} concentrations approximated 0.264 and 0.047 μg TCDD/kg body weight/day, respectively, for the two lengths of dosing.

In adult female mink exposed to 5 ng/g TCDD for 6 months, the maxilla and mandible were grossly unremarkable, but histologically they had nests of squamous epithelium within the periodontal ligament. There was osteolysis of the adjacent alveolar bone.[418] In a study of 12-week-old male mink fed 24 ng/g PCB 126 for 31–69 days, similar symptoms developed, including thickened gingiva and loose teeth. Squamous cells proliferated into bone and caused jaw osteoporosis.[419] Rhesus macaques (*Macaca mulatta*) also showed these symptoms.[420] This study was one of the first to address equitoxic doses of congeners and Aroclor mixtures that produced similar effects at different doses, including Aroclors 1242, 1248, PCB 77, PCB126, TCDD, 2,3,7,8-TCDF, and 2,3,4,6,7,8-hexachlorodibenzo-*p*-dioxin. The importance of 1,25-dihydroxy-vitamin D3 in the control of tooth development was linked to vitamin D deficiency in rats; it was concluded that the tooth is a target organ for 1,25-dihydroxyvitamin D3.[421] Calcitonin, estrogen, and parathyroid hormone all interact with vitamin D in the control and deposition of bone and for maintaining tooth health. Aroclor 1254 resulted in smaller body weight and increased urinary alkaline phosphatase and lactate dehydrogenase, serum calcium, nephrotoxicity, and abnormal bone morphometry in young, growing male Fisher 344 rats, but serum PTH, phosphorus, alkaline phosphatase, LDH, and 1,25-dihydroxy vitamin D3 were unchanged at any dose.[422] The influence of the dioxin-like congeners on MFO induction/inhibition, and availability of the above hormones, as well as their effect on carrier and other proteins that direct calcium metabolism and toxic effect in general need further elucidation.

A study of multigenerational effects was conducted on mink in which they consumed PCB-contaminated carp from Saginaw Bay, Lake Huron.[423] The adult mink were fed diets formulated to provide 0 (control), 0.25, 0.5, or 1.0 μg/g PCBs through substitution of Saginaw Bay carp for ocean fish in the diet. Continuous F1 exposures to = 0.25 μg/g of PCBs delayed the onset of estrus (as determined by vulvar swelling and time of mating) and lessened the whelping rate. Litters whelped by females continuously exposed to = 0.5 μg/g of PCBs had greater mortality and lower body weights than did controls. Continuous exposure to 1.0 μg/g PCBs had a variable effect on serum thyroxin (T4) and triiodothyronine (T3) concentrations. There were significant differences in kidney, liver, brain, spleen, heart, and thyroid gland weights of the mink continuously exposed to 1.0 μg/g PCBs.

Plasma and liver PCB concentrations of the adult and kit mink were, in general, directly related to the dietary concentration of PCBs and the duration and time of exposure. Short-term parental exposure to PCBs had detrimental effects on survival of subsequent generations of mink, conceived months after the parents were placed on "clean" feed. The LOAEL for use of an environmentally weathered PCB diet in this study was 0.25 µg/g. Using a similar Saginaw Bay carp feeding protocol in a one-generation test, Tillitt and co-workers[262] estimated a total TCDD toxicity equivalent concentration threshold dietary dose of 1.9 pg/g and 60 pg/g_{liver} for adult mink that had been exposed and chemically analyzed. According to earlier WHO mammalian TEFs,[258,259] PCBs contributed approximately 76 to 82% of dietary total TCDD equivalents, while in livers of adult mink, PCBs accounted for 61 to 65% of total TCDD equivalents. Since absorbed concentrations are more relevant in assessment of target organ and reproductive effects, liver concentrations of the latter are more ecotoxicologically important. Rank-ordered contributors to total TCDD equivalent concentrations, from highest to lowest, were PCB126, 2,3,7,8-TCDD, 2,3,7,8-TCDF, 2,3,4,7,8-PeCDF, and PCB 118.

Across dosage groups, PCB 126 was at least fivefold more potent as a contributor to total TEQ concentrations in mink liver than either 2,3,7,8-TCDD or 2,3,7,8-TCDF. These relative importance rankings will vary because ecosystems, on a site-specific scale, have been polluted with different congener ratios from different sources. The new WHO TEFs[257] would increase the overall importance of the PCDDs in this study slightly due to the change of TEF for 1,2,3,7,8-PCDD from 0.5 to 1.0. Chronic effects in adult mink dosed in this study are addressed in a companion paper[424] and are consistent with previous work using known quantities of commercial PCB mixtures. In a study of the risk to Great Lakes fish contaminated with PCBs, virtually every fish species potentially consumed by mink offered some measure of risk.[425]

Other Mammals — Common seal populations in the Wadden Sea in The Netherlands appear to have declined due to PCBs.[426,427] Effects on the uteri of Baltic ringed seals have been noted when levels of DDT and PCB are higher than in normal females. The same effect was observed in Baltic grey seals (*Halichaerus grypus*) when concentrations of PCB were > 70 µg/g in blubber fat, and they were not fertile at these concentrations. High PCDD and PCDF levels were also correlated with the high PCBs in these species, suggesting that these compounds may actually be responsible for these reproductive problems.

It has been suggested that PCBs may affect bats.[428,429] Reinhold and associates[430] studied the pond bat (*Myotis dasycneme*) and its major food source, chironomids. They found that PCBs measured in chironomids did not exceed "safe" dietary levels for mammals. Nonetheless, some bats had PCB concentrations of 9, 33, or 76 mg kg-1 lipid weight, which exceed the concentration levels that cause reproductive effects in mink. Further work on bats appear mandatory since several bat species are federally listed species in the United States.

For additional information on the exposure to and the effects of PCBs, PCDDs, and PCDFs on aquatic and marine mammals, some excellent recent reviews can be consulted.[431–433] Another recent review provided analysis of tissue and dietary thresholds for various aquatic mammals.[434] Threshold PCB or TCDD-equivalent concentrations in livers of aquatic mammals that elicited physiological effects ranged from 6.6 to 11 µg PCBs/g (geometric mean: 8.7 µg/g) and 160 to 1400 pg TCDD equivalents (geometric mean: 520 pg/g) for lipid weight, respectively. Biomagnification factors for PCBs and TCDD equivalents varied by species of marine mammal. The dietary threshold concentration ranges for these marine mammals were 10 to 150 ng PCBs/g and 1.4 to 1.9 pg TEQs/g wet weight.

18.6.4.4 Endocrine and Mixed Function Oxidase Effects

There is a dearth of information on wild mammals concerning MFO induction, and little more information is available concerning their immune systems. Controlled studies are extremely difficult

to conduct, especially for large marine mammals. Concern over the use of larger mammals in testing is also evident from this paucity of information. As with the preceding discussion on chronic effects, key reviews should be consulted to assess what is available.[431–433]

Seals — Harbor seals fed fish from the Wadden Sea (high-level PCB contamination) had significantly lower concentrations of plasma retinol, total thyroxin (TT4) and free thyroxin (FT4), and total triiodothyronine (TT3). The PCB-induced reduction in plasma retinol levels disappeared when seals on a diet of Wadden Sea fish were subsequently fed low-PCB-containing Atlantic Ocean fish. The authors suggested that an increased susceptibility to microbial infections, reproductive disorders, and other pathological alterations were related to reproductive disorders and to the lethal viral infections in seals and other marine mammal populations in the Baltic Sea, North Sea, and Wadden Sea. The reduced plasma retinol and thyroid hormone levels were implicated.[435] Subsequently, a comprehensive review of the seal problem and concerns for their protection was produced in 1992, which included a suggestion to perform feeding experiments with mink as a surrogate species for studying the problem.[436]

In an additional report on these harbor seals, impairment of T-cell-mediated immune responses became apparent during the second year on the Wadden Sea/Atlantic Ocean fish diets used earlier and correlated significantly with TCDD equivalent levels in blubber biopsies taken from the seals after 2 years. Humoral immune responses remained largely unaffected. The authors concluded that cellular immune system suppression response in seals fed a third diet of Baltic herring was induced by the chronic exposure to immunotoxic environmental contaminants accumulated through the food chain and could be of crucial importance in the clearance of morbillivirus (canine distemper virus) infections. Environmental-pollution-related immunosuppression may have contributed to the severity and extent of recent morbillivirus-related mass mortalities among marine mammals.[437] More recently, total PCBs in the blubber and liver of harbor seals were correlated with P450, P420, and MFO activity levels.[438]

Harbor seals assessed from southern San Francisco Bay had a mean whole-blood PCB concentration of 50 ng/mL, about three times the average level reported for blood of captive seals fed exclusively on fish from the Baltic's PCB-contaminated Wadden Sea. These findings support concerns about the ecological effects of PCB contamination in San Francisco Bay.[439] Four-week-old harbor seal pups from coastal California had mean PCB concentrations in blubber of 3.3 μg/g on a lipid basis.[440] This study demonstrated that contaminated pups exhibited relatively strong lymphocyte proliferative response to conconavalin A and moderate responses to poke weed mitogen and phytohemagglutinin. Serum thyroid hormone levels in the pups were typical for levels reported in neonatal seals. Regression analysis revealed associations between reduced immune responses and increasing levels of TCDD equivalents (non-*ortho* PCBs were 46% of the total), suggesting an effect of planar PCBs on T-cell function. Reduced thyroid hormone levels were associated with increasing levels of TCDD equivalents, suggesting the involvement of planar and nonplanar congeners. The estimated threshold for immune- and endocrine-disrupting effects of bioactive PCB congeners was 3 μg/g on a lipid basis for neonatal harbor seals.

The situation for the Baltic grey seal was recently reviewed. It has seen general improvement in reproductive and other parameters between 1977 and 1996, but there is an increase in colonic ulcers in young grey seals, suggesting the possibility of another new contaminant in this ecosystem.[441] The disease complex comprised lesions of claws, skull bone, intestine (colonic ulcers), kidneys (glomerulopathy, tubular cell proliferations), arteries (sclerosis) and adrenal glands (cortical hyperplasia, cortical adenomas). Besides occlusions and stenoses, tumors (leiomyomas) were common in the uterus. A time trend of improving gynecological health with decreasing PCBs and DDT was confirmed.

Mink — In a study of mink from the Frazer and Columbia River systems in the Pacific Northwest of North America, juvenile mink demonstrated a significant negative correlation between total PCB

concentrations in the liver and baculum length. The association of juvenile baculum length with eventual reproductive success is unknown at the present time.[442] There is supportive evidence for these types of responses occurring in other mammals as follows: dosing of adult rats with PCB 169 produced male offspring that had reduced ventral prostate, seminal vesicles, testes weights, epididymides, and sperm counts and were in general considered to be slow in all maturation events including time to puberty. Delayed development in this sense was not considered an antiandrogenic response because hallmark effects of reduced anogenital distance, male hypospadias, or induction of areolas or nipples did not occur.[443] However, as 600-day-old adults, these PCB 169-exposed offspring had ventral prostates, caudal sperm counts, and ejaculated sperm counts that were all significantly reduced, and there was a significant increase in dorsolateral lobe prostatitis.

Polar Bear — In a recent comprehensive review from Canada, the species with the most significant risk of exposure to PCBs and organochlorine (OC) pesticides appeared to be the polar bear (*Ursus maritimus*). In this study, the measured EROD function in the polar bear appeared to have elevated CYP1A-mediated activity, relative to beluga whale (*Delphinapterus leucas*) and ringed seal. The MFO enzyme data for polar bear, beluga, and seal suggest that even the relatively low levels of contaminants present in Arctic animals may not be without biological effects, especially during years of poor feeding.[444] The PCDD/PCDF congener pattern in polar bear milk from Svalbard, Norway was different from that found in polar bear fat from the Canadian Arctic, although non-*ortho*-substituted PCBs in polar bear milk were similar to those found in polar bear fat from the Canadian North.[445] In 1996, two yearling polar bears at Svalbard, Norway were captured that were found to have a normal vaginal opening and a 20-mm penis containing a baculum. The penis was located caudal to the location in a normal male and was concealed within the vaginal opening by a single pair of labia. Neither of the yearlings showed signs of a Y chromosome, so both bears were regarded as female pseudohermaphrodites. Two additional bears with aberrant genital morphology and a high degree of chloral hypertrophy at Svalbard were also classified as female pseudohermaphrodites. The observed rate of female pseudohermaphroditism in this area was 1.5% (4/269). Pseudohermaphroditism in this polar bear population could result from excessive androgen excretion by the mother, be caused by a tumor, or be the result of endocrine disruption from environmental contaminants.[446] A recent compilation of contamination and effects has been produced covering the Svalbard area.[447]

Whales and Dolphins — The Gulf of St. Lawrence beluga whales have received considerable attention as a population of which approximately 500 individuals remain. It is not expanding, suggesting reduced reproduction and survival of juveniles. Of all of the tumors reported in cetaceans, 37% were observed in these whales. An adult hermaphrodite beluga has been documented, with two ovaries, two testes, and complete genital tracts of both sexes, with the exception of cervix, vagina, and vulva. Belugas are contaminated with a wide mix of endocrine-disruptive and carcinogenic contaminants. So far no attempts have been made to identify any likely causative agents from the large family of pollutants to which the belugas are exposed.[448] Bottlenose dolphins (*Tursiops truncatus*) have a reduced *in vitro* mitogen response to Con A and PHA that is associated with increased levels of PCBs and DDT in peripheral blood.[449]

18.6.4.5 Invertebrates and Other Aquatic Organisms

18.6.4.5.1 Invertebrates

Barber and co-workers[450] found no indication of 2,3,7,8-TCDD toxicity to survival or growth in the amphipod (*Ampelisca abdita*), using spiked sediments from coastal New Jersey waters with a range of 2,3,7,8-TCDD concentrations (0–25 μg/kg dry weight). The maximum 2,3,7,8-TCDD concentration in ambient sediment was 0.62 μg/kg. Ashley and co-workers[451] reported a 2,3,7,8-

TCDD LD_{50} of 30–100 μg/kg for freshwater crayfish (*Pacifastacus leniusculus*), with a delayed mortality of typically 15–40 days after dosing, and anergia. These authors reported that treatment of crayfish with 3 μg/kg of TCDD significantly induced cytochrome P450, as measured spectrally, and that induction and delayed onset of mortality suggested the presence of a receptor-mediated mechanism of TCDD toxicity in crayfish. Hahn and co-workers[452] and Powell and co-workers[453] provide useful information on, respectively, the possible evolutionary precursor of the Ah receptor in invertebrates and the discovery of an ortholog Ah receptor in the invertebrate nematode *Caenorhabditis elegans*.

Acute PCB doses vary by organism, ranging from 10,000 μg/g for hydra[454] to 1.3 μg/L for 121-day exposure of *Daphnia magna*.[455] Crayfish, damselfly, glass shrimp, and stonefly were also tested.[64] Marine invertebrates have been tested; shrimp (Grass, Brown, and Pink) had LD_{50}s of 6.1 to 12.5 μg/g.[328,456]

Several reports of decreased growth of aquatic organisms during exposure to PCBs can be found in the literature. For example, diatoms were affected at 0.1 μg/L Aroclor 1254, and oysters were affected at 10 μg/L Aroclor 1016. These concentrations are much higher than are usually encountered in the environment today. When sediment is chemically characterized, various comparative "effects thresholds" have been assessed for invertebrate toxicity.[456] A consensus-based probable effects threshold was calculated to be 676 μg/kg sediment, expressed on a dry-weight basis. This value is relevant for invertebrate species that have been tested and do not apply to other animal classes in which PCBs and related compounds bioaccumulate and biomagnify to higher trophic levels.

18.6.4.5.2 Other Aquatic Organisms

There is little definitive information on reptiles and amphibians. Snapping turtles have received considerable attention. Studies on the Northern leopard frog have not found the species to be sensitive to dioxin-like exposures; effects studied include PCB 126 MFO induction,[457] EROD activity and feral carcass PCB concentration,[458] PCB 126 weight loss, and growth rate.[459] These results are consistent with the resistance of the bullfrog to TCDD.[235,282] Contaminant reviews that have addressed reptiles and amphibians should be consulted.[460,461]

18.7 SUMMARY

PCBs, PCDDs, and PCDFs are all similar in their chemistry, i.e., aromatic rings with varying degrees of chlorination. The dioxins and dibenzofurans differ in the fact that they all have a bridge oxygen substituted across adjoining phenyl rings. The chemistry, fate, and effects of these compounds are very complex. This complexity arises primarily from the fact that these compounds exist as complex mixtures. PCBs are composed of a large number of compounds (usually 100–150 separate congeners) that require specialized methods of analysis. In the dioxin and dibenzofuran class of compounds, there are fewer isomers. However, there is the added problem of the extreme toxicity of these compounds, requiring methods for analysis and detection down to levels of picogram-per-gram concentration.

PCBs are universally distributed throughout the world, a fact largely resulting from their considerable aquatic and atmospheric mobility. Much of the release of these chemicals occurred over the span of their industrial use, from 1930 until the late 1970s, primarily as electrical insulating compounds and as hydraulic fluids. Numerous hot spots exist even today, over 20 years after the compounds were banned by the United States in 1977. Because of the extensive use of PCBs in electrical devices, indoor air levels of PCBs still exceed their levels in most outside air. Initial releases most often occurred into aqueous systems; however, atmospheric losses, especially from aquatic systems, are important for the dispersal of PCBs to remote systems such as the Arctic.

Levels in the air have begun to stabilize, to the point where ambient concentrations in Great Lakes water now degas into the atmosphere rather than continually load from the air, as was the situation in earlier times.

PCBs are noted for their tendency to bioaccumulate in aquatic and terrestrial organisms. This accumulation is a function of the compounds' partitioning behaviors, with increasing buildup accompanying greater chlorine substitution. Empirical data for terrestrial accumulation show the importance of diet and location, especially for caribou in the Arctic. Models for accumulation by dairy cows show the importance of atmospheric accumulation into forage crops and how lipid association and metabolism can be used to explain accumulation levels and possible human exposure. Abiotic dispersal of PCBs is sufficient to explain most of what we know about the existing placement of the world's supply of PCBs. The mobile environmental reservoir for PCBs is largely in the oceans (87%), followed by freshwater sediments, water, and biota (9.9%). How the compounds have distributed themselves in these compartments depends mostly on their physicochemical properties.

The air–water exchange behavior of PCBs has helped modelers to better explain existing levels in large bodies of water, particularly the Great Lakes. The soil reservoir and soil-to-air transfer have been widely recognized as important in maintaining existing levels in rural and metropolitan areas, especially in the United Kingdom. Long-term monitoring of PCBs in air is being used in the Great Lakes and other areas to identify sources. In water, adsorption to sediment or other organic matter is an important fate process for PCBs. Several sites with high- PCB sediment concentrations are being considered for mitigation; one of the most extensively contaminated sites is the upper Hudson River in New York State. Decreasing concentrations of PCBs in biota are beginning to be observed at locations throughout the world. Both aerobic and anaerobic degradation of PCBs have been described. Generally, the overall changes in levels due to degradation are slight, except for processes involving atmospheric photolysis.

During the late 1960s and early 1970s, it was recognized that PCDDs and PCDFs could be formed as by-products during the manufacture of various classes of chlorinated organic chemicals e.g., PCDFs from PCBs and PCDDs/PCDFs from chlorophenols. Since in most industrialized countries the manufacture and use of PCBs have been terminated and chlorophenol use has been severely restricted, emissions from the combustion of municipal wastes are currently the most important sources of PCDDs/PCDFs in the environment. However, diffuse sources such as domestic heating and outdoor trash burning are assuming greater relative importance, as controls are being implemented on municipal incinerators.

On a global scale, estimates of the quantity of deposited PCDDs/PCDFs exceed emissions estimates from combustion by a factor of two to three. Recently it has been proposed that the discrepancy could be accounted for by the photochemical formation of the two major atmospheric PCDDs/PCDFs, heptaCDD and OCDD, from pentachlorophenol in cloud water. While the photochemical process is an alternate pathway for the formation of PCDDs/PCDFs, controls that have been placed on chemical manufacturing and combustion emissions have resulted in significant declines in PCDDs/PCDFs in aquatic, atmospheric, and terrestrial environments. In the 1980s, it was found that biota in large bodies of water receiving industrial discharges, such as the Great Lakes and the Baltic Sea, were contaminated with PCDDs and PCDFs. Concentrations of 2,3,7,8-TCDD in fish from Lake Ontario varied from 2 pg/g for brown bullhead, a planktivorous fish species, to 162 pg/g for brown trout, a piscivorous species. In 1994, no 2,3,7,8-TCDD was detected at limits of detection of 1–2 pg/g in nine fish collected from Lake Ontario, including salmon, walleye, and perch. Similar improvements have been found for other aquatic species. During the same time period, ambient atmospheric concentrations of PCDDs/PCDFs declined by a factor of two in major European cities; current levels generally do not exceed 10 pg/m.[3]

The ability to address the effects of these three structurally and toxicologically related groupings of halogented organics has greatly improved, especially over the last 10 years. Exposures of test organisms have demonstrated that, for classic measurement endpoints, a given species will respond

identically to different dioxin-like congeners when exposure is adjusted to compensate for their different toxic potencies. Use of a combination of relative toxic potency to produce a multitude of measurement endpoints and an additive model of toxicity for the dioxin-like components of the PCBs, PCDDs, and PCDFs have dramatically improved our ability to interpret environmental residues along with representative biological and toxicological responses to a variety of organisms.

Across animal taxa and on a number of levels, there are differences in relative sensitivity to these exposures. Mammal, bird, and fish species may be either highly sensitive or highly resistant to dioxin-like adverse effects, especially chronic reproductive and developmental/endocrine effects. Aquatic food chain species (seals, dolphins, polar bears, piscivorous birds, and cold-water fish species) with high exposure potential through biomagnification are particularly vulnerable to such effects. Invertebrates are relatively insensitive because they lack an Ah receptor. Ecological effects of PCDDs, PCDFs, and PCBs have manifested and continue to manifest in areas where such compounds have been documented historically at high concentrations. Environmental effects can remain for long periods because of ecosystem dynamics and the persistence of these chemicals. Continued study of nondioxin-like congeners, especially with PCBs, is needed across animal taxa. The reporting of total PCBs from the summation of congener-specific analyses, as well as the reporting of individual congeners, is also important because of the large abundance of nondioxin-like PCB congeners in the original commercial mixtures and in environmental samples.

REFERENCES

1. Bremer, K. E., Dealing with multi-agency and multi-state regulation of polychlorinated biphenyls, in PCBs, in *Human and Environmental Hazards,* D'Itri, M. and Kamrin, M. A., Eds., Butterworth Publishing, Woburn, MA, 1983, 367
2. Kuratsune, M., Yoshimura, T., Matsuzaha, J., and Yamaguchi, A., Epidemiological study of Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls, *Environ. Health Perspect.* 1, 119, 1972.
3. Durfee, R. L., Contos, G., Whitmore, C., Barden, J. D., Hackman, E. E., III, and Westin, R. A., PCBs in the United States — Industrial Use and Environmental Distribution, Versar, Springfield, VA, 1976.
4. Huntzinger, O. S. and Safe, Z. V., *The Chemistry of PCBs,* CRC Press, Boca Raton, FL, 1974.
5. Ballschmiter, K. and Zell, M., Analysis of polychlorinated biphenyls (PCB) by glass capillary gas chromatography, *Fresenius Zeitschrift für Anal. Chem.* 302, 20, 1980.
6. U.S. EPA, *Region v. PCB ID, BZ v. IUPAC,* Comparison of PCB Nomenclature — Past and Present, 2000.
7. Huehnerfuss, H., Pfaffenberger, B., Gehrcke, B., Karbe, L., Koenig, W. A., and Landgraff, O., Stereochemical effects of PCBs in the marine environment: Seasonal variation of coplanar and atropisomeric PCBs in blue mussels (*Mytilus edulis* L.) of the German Bight, *Mar. Pollut. Bull.*, 30, 332, 1995.
8. Jimenez, O., Jimenez, B., Marsili, L., and Gonzalez, M. J., Enantiomeric ratios of chiral polychlorinated biphenyls in stranded cetaceans form the Mediterranean Sea, *Organohalogen Compd.*, 40, 409, 1999.
9. Wong, C. S. and Garrison, A. W., Enantiomer separation of polychlorinated biphenyl atropisomers and polychlorinated biphenyl retention behavior on modified cyclodextrin capillary gas chromatography columns, *J. Chromatogr. A,* 866, 213, 2000.
10. McConnell, E. E., Acute and chronic toxicity and carcinogenesis, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds,* Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 1989, Chap. 6.
11. Neubert, D., Peculiarities of the toxicity of polyhalogenated dibenzo-*p*-dioxins and dibenzofurans in animals and man, *Chemosphere,* 23, 1869, 1991.
12. Stehl, R. H., Papenfuss, R. R., Bredeweg, R. A., and Roberts, R. W., The stability of pentachlorophenol and chlorinated dioxins to sunlight, heat and combustion, in *Chlorodioxins — Origin and Fate,* Blair, E. H., Ed., Advances in Chemistry Series 120, American Chemical Society, Washington, D.C., 1973, Chap. 13.

13. Pohland, A. E. and Yang, G. C., Preparation and characterization of chlorinated dibenzo-*p*-dioxins, *J. Agric. Food Chem.*, 20, 1093, 1972.
14. Crosby, D. G., Wong, A. S., Plimmer, J. R., and Woolson, E. A., Photodecomposition of chlorinated dibenzo-*p*-dioxins, *Science*, 173, 748, 1971.
15. Friesen, K. J., Muin, C. G., and Webster, G. R. B., Evidence of sensitized photolysis of polychlorinated dibenzo-p-dioxins in natural waters under sunlight conditions, *Environ. Sci. Technol.*, 24, 1739, 1990.
16. Brubaker, W. W., Jr. and Hites, R. A., Gas-phase oxidation products of biphenyl and polychlorinated biphenyls, *Environ. Sci. Technol., 32, 3913, 1998.*
17. Marple, L., Brunck, R., and Throop, L., Water solubility of 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin, *Environ. Sci. Technol.*, 20, 180, 1986.
18. Lodge, K. B., Solubility studies using a generator column for 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin, *Chemosphere*, 18, 933, 1989.
19. Lodge, K. B. and Cook, P. M., Partitioning studies of dioxin between sediment and water: The measurement of K_{oc} between sediment and water, *Chemosphere*, 19, 439, 1989.
20. Erickson, M. D., *Analytical Chemistry of PCBs,* CRC Press/Lewis Publishers, Boca Raton, FL, 1997.
21. NAS/NRC, *Polychlorinated Biphenyls,* National Academy of Sciences/National Research Council, Washington, D.C., 1979.
22. Albaiges, J., *Environmental Analytical Chemistry of PCBs,* Gordon and Breach Science Publishers, Yverdon, Switzerland, 1993.
23. Dobson, S. and van Esch, G. J., *Polychlorinated Biphenyls and Terphenyls,* World Health Organization, Geneva, Switzerland, 1993.
24. Strachan, W. M. J., Polychlorinated Biphenyls (PCBs): Fate and Effects in the Canadian Environment, Environment Canada, Environmental Protection Service, Ottawa, Canada, 1988.
25. American Council on Science and Health, *PCBs, Is the Cure Worth the Cost?*, The Council, Summit, NJ, 1986.
26. Hansen, L. G., *The Ortho Side of PCBs: Occurrence and Disposition*, Kluwer Academic, Boston, 1999.
27. ATSDR, Toxicological Profile for Polychlorinated Biphenyls (Update), U.S. Dept. of Health and Human Services, Public Health Service, Washington, D.C., 1997
28. EDSTAC, Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) Final Report, U.S. EPA, Washington, D.C., 1998.
29. Hettling, L. J., Horn, E. G., and Tofflemier, T. J., Summary of Hudson River PCB study results, Dept. of Environmental Conservation, Albany, NY, 1978.
30. Rice, C. P., and White, D. S., PCB availability assessment of river dredging using caged clams and fish, *Environ. Toxicol. Chem.*, 6, 4, 259, 1987.
31. U.S. EPA, Superfund Record of Decision (EPA Region 1): (First Remedial Action), Report, EPA/ROD/R01–90/045 (PB90–254293), New Bedford, MA, 251, March 1990.
32. Hwang, S. A., Gensburg, L. J., Fitzgerald, E., Herzfeld, P. M., and Bush, B., Fingerprinting sources of contamination: Statistical techniques for identifying point sources of PCBs, *J. Occup. Med. Toxicol.*, 2, 4, 365–382, 1993.
33. Stratus Consulting, *Stage I Assessment Plan, Kalamazoo River Environment Site*, Stratus Consulting, Boulder, CO, 2000.
34. Sullivan, J. R. and Delphino, J. J., *A Select Inventory of Chemicals Used in Wisconsin's Lower Fox River Basin*, WIS-SG-82–238, University of Wisconsin Sea Grant Institute, Madison, WI, 1982.
35. U.S. EPA, Office of Water, USEPA Fisheries Advisory Report 1998, EPA-823-PCDF-99–005, 99, 2001.
36. Fuller, K., Shear, H., and Wittig, J., The Great Lakes: An Environmental Atlas and Resource Book, United States Environmental Protection Agency and Government Canada, Great Lakes National Program Office/Environment Canada, Chicago Illinois/Downsview, Ontario, Canada, 1995
37. Bopp, R., Simpson, H. J., Deck, B. L., and Kostyk, N., The persistence of PCB components in sediments of the lower Hudson, *Northeast. Environ. Sci.*, 3, 180, 1984.
38. Ikalainen, A. J. and Allen., D. C., New Bedford Harbor Superfund Project, in *Contaminated Marine Sediments: Assessment and Remediation,* Edited by National Research Council, Committee on Contaminated Sediment, National Academy Press, Washington, D.C., 1989, 365.
39. Sanders, J. E., PCB pollution in the Upper Hudson River, in *Contaminated Marine Sediments: Assessment and Remediation*, Edited by National Research Council, Committee on Contaminated Sediment, National Academy Press, Washington, D.C., 1989, 496.

40. Sanders, J. E., PCB pollution problem in the Upper Hudson River: From environmental disaster to environmental gridlock, *Northeast. Environ. Sci.*, 8, 1, 1989.
41. Pavlou, S. P., Environmental dynamics of trace organic contaminants in estuarine and coastal zone ecosystems, in *Analytical Techniques in Environmental Chemistry*, Albaiges, J., Ed., Pergamon Press, New York, 1980, 387.
42. Ashley, J.T. and Baker, J. E., Hydrophobic organic contaminants in surficial sediments of Baltimore Harbor: Inventories and sources, *Environ. Toxicol. Chem.*, 18, 5, 838, 1999.
43. Anon., Superfund Record of Decision (EPA Region 1): New Bedford Site, Upper and Lower Harbor Operable Units, New Bedford, MA, September 25, 1998. Govt. Reports Announcements & Index (GRA&I) Issue 14 (PB98–963709), 344, 1999.
44. Bergen, B. J., Rahn, K. A., and Nelson, W. G., Remediation at a marine superfund site: Surficial sediment PCB congener concentration, composition, and redistribution, *Environ. Sci. Tech.*, 32, 22, 3496, 1998.
45. Bremle, G., Larsson, P., Hammar, T., Helgee, A., and Troedsson, B., PCB in a river system during sediment remediation, *Water Air Soil Pollut.*, 107, 1–4, 237, 1998.
46. U.S. EPA, Region II, Draft Joint Supplement to the Final Environmental Impact Statement on the Hudson River PCB Reclamation Demonstration Project, USEPA, USEPA, Region II, New York,/New York State Department of Environmental Conservation, Albany, 1987.
47. Eisenreich, S. J., Looney, B. B., and Thornton, B. B., Airborne organic contaminants in the Great Lakes ecosystem, *Environ. Sci. Technol.*, 15, 30, 1981.
48. Swackhamer, D. L., Studies of polychlorinated biphenyls in the Great Lakes, in *Chlorinated Organic Micropollutants*, Hester, R. E. and Harrison, R. M., Eds., London: Royal Society of Chemistry, 1996, 137–153.
49. Strachan, W. M. J. and Eisenreich, S. J., Mass balance accounting of chemicals in the Great Lakes, in *Long Range Transport of Pesticides*, Kurz, J., Ed., Lewis Publishers, Chelsea, MI, 1990, 291–301.
50. Jeremiason, J. D., Hornbuckle, K. C., and Eisenreich, S. J., PCBs in Lake Superior, 1978–1992: Decreases in water concentrations reflect loss by volatilization, *Environ. Sci. Technol.*, 28, 903, 1994.
51. Mamontov, A. A., Mamontova, E. A., Tarasova, E. N., and McLachlan, M. S., Tracing the sources of PCDD/PCDFs and PCBs to Lake Baikal, *Environ. Sci. Technol.*, 34, 741, 2000.
52. Iwata, H., Tanabe, S., Ueda, K., and Tatsukawa, R., Persistent organochlorine residues in air, water, sediments, and soils from the Lake Baikal region, Russia, *Environ. Sci. Technol.*, 29, 3, 792, 1995.
53. Tanaba, S., Distribution, behavior and fate of PCBs in the marine environment by the member awarded the Okada prize of the Oceanographical Society of Japan for 1985, *J. Oceanogr. Soc. Jpn.*, 41, 358, 1985.
54. de March, B. G. E., deWitt, C. A., and Muir, D. C, G., Persistent organic pollutants, in *AMAP Assessment Report: Arctic Pollution Issues*, Wilson, S. J., Murray, J. L., and Huntington, H. P., Eds., Arctic Monitoring and Assessment Programme (AMAP), Oslo, Norway, 1998, 183–371.
55. Wania, F. and Mackay, D., Tracking the persistence of persistent organic compounds, *Environ. Sci. Technol.* 30, 390A, 1996.
56. Sweetman, A. J. and Jones, K. C., Declining PCB Concentrations in the U.K. atmosphere: Evidence and possible causes, *Environ. Sci. Technol.*, 34, 5, 863, 2000.
57. Harrad, S. J., Sewart, A. P., Alcock, R., Boumphrey, R., Burnett, V., Duarte, D. R., Davidson, R., Halsall, C., Sanders, G., Waterhouse, K., Wild, S. R., and Jones, K. C., Polychlorinated biphenyls (PCBs) in the British environment: Sinks, sources and temporal trends, *Environ. Pollut.*, 85, 131, 1994.
58. MacLeod, K. E., Polychlorinated biphenyls in indoor air, *Environ. Sci. Technol.*, 15, 926, 1981.
59. Wallace, J. C., Basu, I., and Hites, R. A., Sampling and analysis artifacts caused by elevated indoor air polychlorinated biphenyl concentrations, *Environ. Sci. Technol.*, 30, 9, 2730, 1996.
60. Currado, G. M. and Harrad, S. A., Factors influencing atmospheric concentrations of polychlorinated biphenyls in Birmingham, U.K., *Environ. Sci. Technol.*, 34, 1, 78, 2000.
61. Gabrio, T., Piechotowski, I., Wallenhorst, T., Klett, M., Cott, L., Friebel, P., Link, B., and Schwenk, M., PCB-blood levels in teachers, working in PCB-contaminated schools, *Chemosphere*, 40, 1055, 2000.
62. Matthews, H. B. and Dedrick, R. L., Metabolism of PCBs, *Annu. Rev. Pharmacol. Toxicol.*, 24, 85, 1984
63. Safe, S., Metabolism, uptake, storage and bioaccumulation, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*, Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier/North Holland Biomedical Press, New York, 1989, Chap. 5.

64. Eisler, R., Polychlorinated biphenyl hazards to fish, wildlife and invertebrates: A synoptic review, Fish and Wildlife Service, U.S. Dept. of the Interior, Washington, D.C., 1986.
65. Gobas, A.P.C., Assessing bioaccumulation factors of persistent organic pollutants in aquatic food-chains, in *Persistent Pollutants: Environmental Behavior and Pathways of Human Exposure,* Harrad, S., Ed., Kluwer Academic Publishers, Norwell, MA, 2001, Chap. 6.
66. Gobas, A. P. C., Graggen, M. N., and Zhang, X., Time response of the Lake Ontario ecosystem to virtual elimination of PCBs, *Environ. Sci. Technol.*, 29, 8, 2038, 1995.
67. Vodicnik, M. J. and Peterson, R. E., The enhancing effect of spawning on elimination of a persistent polychlorinated biphenyl from a female yellow perch, *Fundam. Appl. Toxicol.*, 5, 770, 1985.
68. Wasserman, M., Wassermann, D., Cucos, S., and Miller, J. H., World PCBs map: Storage and effects, in *Man and His Biologic Environment in the 1970s, Ann. N.Y. Acad. Sci.*, 1979, 320.
69. Moessner, S. and Ballschmiter, K., Marine mammals as global pollution indicators for organochlorines, *Chemosphere,* 34, 1285, 1997.
70. Custer, T. W., Sparks, D. W., Sobiech, S. A., Hines, R. K., and Melancon, M. J., Organochlorine accumulation by sentinel mallards at the Winston-Thomas sewage treatment plant, Bloomington, Indiana, *Arch. Environ. Contam. Toxicol.*, 30, 163, 1996.
71. Bowerman, W. W. et al., PCB concentrations in plasma of nestling bald eagles from the Great Lakes Basin, North America, *Organohalogen Compd.*, 4, (Misc. Contrib.), 203, 1990.
72. McCarty, J. P. and Secord, A. L., Reproductive ecology of tree swallows, Tachycineta bicolor) with high levels of polychlorinated biphenyl contamination, *Environ. Toxicol. Chem.*, 18, 1433, 1999.
73. Braune, B., Muir, D., DeMarch, B., Gamberg, M., Poole, K., Currie, R., Dodd, M., Duschenko, W., Eamer, J., Elkin, B., Evans, M., Grundy, S., Hebert, C., Johnstone, R., Kidd, K., Koenig, B., Lockhart, L., Marshall, H., Reimer, K., Sanderson, J., and Shutt, L., Spatial and temporal trends of contaminants in Canadian Arctic freshwater and terrestrial ecosystems: A review, *Sci. Total Environ.*, 230,145, 1999.
74. Elkin, B. T., Organochlorine, heavy metal, and radionuclide contamination transfer through the lichen-caribou wolf food chain, in *Synopsis of research conducted under the Northern Contaminants Program.* Murray, J. L. and Shearer, R. G. Eds., Ottawa: Indian and Northern Affairs Canada, Environmental Studies, 1994, 356–361.
75. Muir, D. C. G., Norstrom, R. J, and Simon, M., Organochlorine contaminants in arctic marine food chains: Accumulation of specific polychlorinated biphenyls and chlordane-related compounds, *Environ. Sci. Technol.*, 22, 1071, 1988.
76. McLachlan, M. S., Model of the Fate of Hydrophobic Contaminants in Cows, *Environ. Sci. Technol.*, 28, 2407, 1994.
77. Sewart, A. and Jones, K. A., A survey of PCB congeners in U.K. cows' milk, *Chemosphere,* 32, 2481, 1996.
78. Thomas, G. O., Sweetman, A. J., and Jones, K. C., Input-output balance of polychlorinated biphenyls in a long-term study of lactating dairy cows, *Environ. Sci. Technol.*, 33, 104, 1999.
79. Sweetman, A. J., Thomas, G. O., and Jones, K. C., Modelling the fate and behaviour of lipophilic organic contaminants in lactating dairy cows, *Environ. Pollut.*, 104, 261, 1999.
80. Calamari, D., Bacci, E., Focardi, S., Gaggi, C., Morosini, M., and Vighi, M., Role of plant biomass in the global environmental partitioning of chlorinated hydrocarbons, *Environ. Sci. Technol.*, 25, 1489, 1991.
81. Hermanson, M. H. and Hites, R. A., Polychlorinated biphenyls in tree bark, *Environ. Sci. Technol.*, 24, 666, 1990.
82. Tanabe, S., PCB problems in the future: Foresight from current knowledge, *Environ. Pollut.* 50, 5, 1988.
83. Boehme, Welsch, P. K., and McLachlan, M. S., Uptake of airborne semivolatile organic compounds in agricultural plants: Field measurements of interspecies variability, *Environ. Sci. Technol.*, 33, 1805, 1999.
84. Muir, D.C., Ford, C. A., Grift, N. P., Metner, D. A., and Lockhart, W. L., Geographic variation of chlorinated hydrocarbons in burbot (*Lota lota*) from remote lakes and rivers in Canada, *Arch. Environ. Contam. Toxicol.*, 19, 530, 1990.
85. Schreitmueller, J. and Ballschmiter, K., Levels of polychlorinated biphenyls in the lower troposphere of the North and South Atlantic Ocean, studies of global baseline pollution XVII, *Fresenius J. Anal. Chem.*, 348, 226, 1994.
86. Zhang, H., Eisenreich, S. J., Franz, T. R., Baker, J. E., and Offenberg, J. H., Evidence for increased gaseous PCB fluxes to Lake Michigan from Chicago, *Environ. Sci. Technol.*, 33, 2129, 1999.

87. Panshin, S. Y. and Hites, R. A., Atmospheric concentrations of polychlorinated biphenyls in Bloomington, Indiana, *Environ. Sci. Technol.*, 28, 2008, 1994.
88. Achman, D. R., Hornbuckle, K. C., and Eisenreich, S. J., Volatilization of polychlorinated biphenyls from Green Gay, Lake Michigan, *Environ. Sci. Technol.*, 27, 75, 1993.
89. Hillery, B. R. and Hites, R. A. Temporal trends in a long-term study of vapor phase PCB concentrations over the Great Lakes, *Organohalogen Compd.*, 28, 536, 1996.
90. Hornbuckle, K. C., Jeremiason, J. D., Sweet, C. W., and Eisenreich, S. J., Seasonal variations in air–water exchange of polychlorinated biphenyls in Lake Superior, *Environ. Sci. Technol.*, 28, 1491, 1994.
91. Thomas, R. G., Volatilization from water, in *Handbook of Chemical Property Estimation Methods*, Lymann, W. J., Reehl, W., and Rosenblatt, D. H., Eds., American Chemical Society, Washington, D.C., 1990, 15-1 to 15-34.
92. Burkhard, L. P., Armstrong, D. E., and Andren, A. W., Henry's law constants for the polychlorinated biphenyls, *Environ. Sci. Technol.*, 19, 590, 1985.
93. Bamford, H. A., Baker, J. E., and Poster, D. L., Review of Methods and Measurements of Selected Hydrophobic Organic Contaminant Aqueous Solubilities, Vapor Pressures, and Air–Water Partition Coefficients, NIST Special Publication 928, National Institute of Standards and Technology, Washington, D.C., 1998.
94. Bamford, H. A., Poster, D. L., and Baker, J. E., Henry's law constants of polychlorinated biphenyl congeners and their variation with temperature, *J. Chem. Eng. Data*, 45, 1069, 2000.
95. Hoff, R. M., Muir, D. C. G., and Grift, N. P., Annual cycle of polychlorinated biphenyls and organohalogen pesticides in air in southern Ontario, 2. Atmospheric transport and sources, *Environ. Sci. Technol.*, 26, 276, 1992.
96. Wania, F., Haugen, J. E., Lei, Y. D., and Mackay, D., Temperature dependence of atmospheric concentrations of semivolatile organic compounds, *Environ. Sci. Technol.*, 32, 1013, 1998.
97. O'Connor, G. A. et al., Plant uptake of sludge-borne PCBs, *J. Environ. Qual.*, 19, 113, 1990.
98. Harner, T., Mackay, D., and Jones, K. C., Model of the long-term exchange of PCBs between soil and the atmosphere in the Southern U.K., *Environ. Sci. Technol.*, 29, 1200, 1995.
99. Taylor, A. W. Volatilization and vapor transport processes, in *Pesticides in the Soil Environment: Processes, Impacts and Modeling*, Cheng, H. H., Ed., Soil Science Society of America Book Series, Madison, WI, 1989, 214–269.
100. Harvey, G. R. and Steinhauer, W. G., Transport pathways of polychlorinated biphenyls in Atlantic water, *J. Mar. Res.*, 34, 561, 1976.
101. Schulz-Bull, D. E., Petrick, G., Bruhn, R., and Duinker, J. C., Chlorobiphenyls (PCBs) and PAHs in water masses of the northern North Atlantic, *Mar. Chem.*, 61, 101, 1998.
102. McConnell, L. L., Kucklick, J. R., Bidleman, T., Ivanov, G. P., and Chernyak, S. M., Air–water gas exchange of organochlorine compounds in Lake Baikal, Russia, *Environ. Sci. Technol.*, 30, 2975, 1996.
103. Ewald, G., Larsson, P., Linge, H., Okla, L., and Szarzi, N., Biotransport of organic pollutants to an inland Alaska Lake by migrating sockeye salmon (*Oncorhynchus nerka*), *Arctic*, 51, 40, 1998.
104. Brownawell, B. J. and Farrington, J. W., Biogeochemistry of PCBs in interstitial waters of a coastal marine sediment, *Geochim. Cosmochim. Acta*, 50, 157, 1986.
105. Hawker, D. W. and Connell, D. W., Octanol–water partition coefficients of polychlorinated biphenyl congeners, *Environ. Sci. Technol.*, 22, 382, 1988.
106. Ballschmiter, K., Rappe, C., and Buser, H. R., Chemical properties, analytical methods and environmental levels of PCBs, PCTs, PCNs and PBBs, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*, Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, New York, Oxford, Amsterdam, 1989, Chap. 2.
107. Ayris, S. and Harrad, S., The fate and persistence of polychlorinated biphenyls in soil, *J. Environ. Monit.*, 1, 395, 1999.
108. Sklarew, D. S., Attenuation of polychlorinated biphenyls in soils, *Rev. Environ. Contam. Toxicol.*, 98, 1, 1997.
109. Callahan, M. A., Slimak, M. W., and Gabel, N. W. Water-related environmental fate of 129 Priority Pollutants, U.S. Environmental Protection Agency, Washington, D.C., 1979, Chap. 36.
110. Anderson, P. N. and Hites, R. A., OH radical reactions: The major removal pathway for polychlorinated biphenyls from the atmosphere, *Environ. Sci. Technol.*, 30, 1756, 1996.

111. Atkinson, R., Atmospheric chemistry of PCBs, PCDDs and PCDFs, *Issues Environ. Sci. Technol.*, 6, 53, 1996.
112. Maltseva, O. V., Tsoi, T. V., Quensen, J., III, Fukuda, M., and Tiedje, J. M., Degradation of anaerobic reductive dechlorination products of Aroclor 1242 by four aerobic bacteria, *Biodegradation*, 10, 363, 1999.
113. Kas, J., Burkhard, J., Demnerova, K., Kostal, J., Macek, T., Mackova, M., and Pazlarova, J., Perspectives in biodegradation of alkanes and PCBs, *Pure Appl. Chem.*, 69, 2357, 1997.
114. Safe, S., Polyhalogenated aromatics: Uptake, disposition and metabolism, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*. Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, New York, Oxford, Amsterdam, 1989, Chap. 5.
115. Schnellmann, R. G., Vickers E. M., and Sipes, I. G., Metabolism and disposition of polychlorinated biphenyls, in *Reviews in Biochemical Toxicology*, Vol. 7, Hodgson, E., Bend, J. R., and Philpot, R. M., Eds., Amsterdam, Elsevier, 1985, 247–282.
116. Sundstrom, G., Hutzinger, O., and Safe, S., The metabolism of chlorobiphenyls, *Chemosphere*, 5, 267, 1976.
117. Bedard, D. L., Unterman, R., Bopp, L. H., Brennan, M. J., Haberl, M. L., and Johnson, C., Rapid assay for screening and characterizing microorganisms for the ability to degrade polychlorinated biphenyls, *Appl. Environ. Microbiol.*, 51, 761, 1986.
118. Brown, J., Wagner R. E., Feng, H., Bedard, D. L., Brennan, M. J., Carnahan, J. C., and May, R. J., Environmental dechlorination of PCBs, *Environ. Toxicol. Chem.*, 6, 579, 1987.
119. Rhee, G. Y., Sokol, R. C., Bethoney, C. M., and Bush, B., Dechlorination of polychlorinated biphenyls by Hudson River sediment organisms: Specificity to the chlorination pattern of congeners, *Environ. Sci. Technol.*, 27, 1190, 1993.
120. Rhee, G. Y., Bush, B., Brown, M. P., Kane, M., and Shane, L., Anaerobic biodegradation of polychlorinated biphenyls in Hudson River sediments and dredged sediments in clay encapsulation, *Water Res.*, 23, 957, 1989.
121. Quensen, J., III, Tiedje, J. M., and Boyd, S. A., Reductive dechlorination of polychlorinated biphenyls by anaerobic microorganisms from sediments, *Science*, 242, 752, 1988.
122. Iwata, Y., Westlake, W. E., and Gunther, A., Varying persistence of polychlorinated biphenyls in six California soils under laboratory conditions, *Bull. Environ. Contam. Toxicol.* 9, 204, 1973.
123. Wakimoto, T., Kannan, N., Ono, M., Tatsukawa, R., and Masuda, Y., Isomer-specific determination of polychlorinated dibenzofurans in Japanese and American polychlorinated biphenyls, *Chemosphere*, 17, 743, 1988.
124. Bowes, G. W., Mulvihill, M. J., Simoneit, B. R. T., Burlingame, A. L., and Risebrough, R. W., Identification of chlorinated dibenzofurans in American polychlorinated biphenyls, *Nature*, 256, 305, 1975.
125. Morita, M., Nakagawa, J., Akiyama, K., Mimura, S., and Isono, N., Detailed examination of polychlorinated dibenzofurans in PCB preparations and Kanemi Yusho oil, *Bull. Environ. Contam. Toxicol.*, 18, 67, 1973.
126. O'Keefe, P. W. and Smith, R. M., PCB capacitor/transformer accidents, in *Halogenated Biphenyls, Naphthalenes, Dibenzodioxins and Related Compounds*, Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 1989, Chap. 15.
127. Woolson, E. A., Thomas, R., and Ensor, P. D. J., Survey of polychlorodibenzo-*p*-dioxin content of selected pesticides, *J. Agric. Food Chem.*, 20, 351, 1972.
128. Buser, H.-R. and Bosshardt, H.-P., Determination of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin at parts per billion levels in technical grade 2,4,5-trichlorophenoxyacetic acid, in 2,4,5-T alkyl ester and 2,4,5-T amine salt herbicide formulations by quadrupole mass fragmentography, *J. Chromatogr.*, 90, 71, 1974.
129. Rappe, C., Buser, H.-R., and Bosshardt, H.-P., Identification and quantification of polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) in 2,4,5-T-ester formulations and herbicide orange, *Chemosphere*, 10, 431, 1978.
130. International Program on Chemical Safety, *Environmental Health Criteria 71: Pentachlorophenols*, World Health Organization, 1987.
131. Buser, H.-R. and Bosshardt, H.-P., Determination of polychlorinated dibenzo-*p*-dioxins and dibenzofurans in commercial pentachlorophenols by combined gas chromatography-mass spectrometry, *J. Assoc. Offic. Anal. Chem.*, 59, 562, 1976.
132. Firestone, D., Chemistry and analysis of pentachlorophenol, *FDA By-Lines*, 8, 57, 1977.

133. Tong, H. Y., Monson, S. J., Gross, M. L., Bopp, R., Simpson, H. J., Deck, B. L. and Moser, C., Analysis of dated sediment samples from the Newark Bay area for selected PCDDs/PCDFs, *Chemosphere*, 20, 1497, 1990.
134. Ehrlich, R., Wenning, R. J., Johnson, G. W., Su, S. H., and Paustenbach, D. J., A mixing model for polychlorinated dibenzo-*p*-dioxins and dibenzofurans in surface sediments from Newark Bay, New Jersey, using polytopic vector analysis, *Arch. Environ. Contam. Toxicol.*, 27, 486, 1994.
135. Pereira, W. E., Rostad, C. E., and Sisak, M. E., Geochemical investigations of polychlorinated dibenzo-*p*-dioxins in the subsurface environment at an abandoned wood-treatment facility, *Environ. Chem. Toxicol.*, 4, 629, 1985.
136. McKee, P., Burt, A., and McCurvin, D., Levels of dioxins, furans and other organics in harbor sediments near a wood processing plant using pentachlorophenol and creosote, *Chemosphere*, 20, 1679, 1990.
137. Kuehl, D. W., Butterworth, B. C., McBride, A., Kroner, S., and Bahnick, D., Contamination of fish by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin: A survey of fish from major watersheds in the United States, *Chemosphere*, 18, 1997, 1989.
138. Axegard, P. and Renberg, L., The influence of bleaching chemicals and lignin content on the formation of polychlorinated dioxins and dibenzofurans, *Chemosphere*, 19, 661, 1989.
139. LaFleur, L., Brunck, B., McDonough, T., Ramage, K., Gillespie, W., and Malcolm, E., Studies on the mechanism of PCDD/PCDF formation during the bleaching of pulp, *Chemosphere*, 20, 1731, 1990.
140. Kuehl, D. W., Butterworth, B. C., DeVita, W. M., and Sauer, C. P., Environmental contamination of polychlorinated dibenzo-*p*-dioxins and dibenzofurans associated with pulp and paper mill discharge, *Biomed. Environ. Mass Spectrom.*, 14, 443, 1987.
141. Chement, R. E., Suter, S. A., Reiner, E., McCurvin, D., and Hollinger, D., Concentrations of chlorinated dibenzo-*p*-dioxins and dibenzofurans in effluents and centrifuged particulates from Ontario pulp and paper mills, *Chemosphere*, 19, 649, 1989.
142. Vanness, G., Tiernan, T. O., Hanes, M. S., Reynolds, C. J., Garrett, J. H., Wagel, D. J., and Solch, J. G., Determination of dibenzo-*p*-dioxin (DBD) and dibenzofuran (DBF) in paper pulp mill defoamer additives and in paper pulp samples, *Chemosphere*, 20, 1611, 1990.
143. Whittemore, R. C., LaFleur, L. E., Gillespie, W. J., Amendola, G. A., and Helms, J., USEPA/paper industry cooperative dioxin study: The 104-mill study, *Chemosphere*, 20, 1625, 1990.
144. MacDonald, R. W., Ikonomou, M. G., and Paton, D. W., Historical inputs of PCDDs, PCDFs, and PCBs to a British Columbia interior lake — The effect of environmental controls on pulp mill emissions, *Environ. Sci. Technol.*, 32, 331, 1998.
145. Hagen, M. E., Colodey, A. G., Knapp, W. D., and Samis, S. C., Environmental response to decreased dioxin and furan loadings from British Columbia coastal pulp mills, *Chemosphere*, 34, 1221, 1997.
146. Krahn, P. K., Dioxins and Furans in British Columbia Pulp Mill Effluent, (1987–1995), Short Papers, Vol. 24, *15th Int. Symp. Dioxins Related Compd.*, Edmonton, Canada, 1995, 217.
147. Eljarrat, E., Caixach, J., and Rivera, J., Decline of PCDD and PCDF in sewage sludges from Catalonia, Spain, *Environ. Sci. Technol.*, 33, 2493, 1999.
148. Jones, K. C. and Sewart, A. P., Dioxins and furans in sewage sludges — A review of their occurrence and sources in sludge and of their environmental fate, behavior, and significance in sludge-amended agricultural systems, *Crit. Rev. Environ. Sci. Technol.*, 27, 1, 1997.
149. NATO/CCMS, International Toxicity Equivalent Factor (I-TEF), Method of risk assessment for complex mixtures of dioxins and related compounds, Pilot study on international information exchange on dioxins and related compounds, Report no. 176, 1988.
150. Villaneuva, E. C., Jennings, R. W., Burse, V. W., and Kimbrough, R. D., Evidence of chlorodibenzo-*p*-dioxin and chlorodibenzofuran in hexachlorobenzene, *J. Agric. Food Chem.*, 22, 916, 1974.
151. Heindl, A. and Hutzinger, O., Search for industrial sources of PCDD/PCDF: III. Short-chain chlorinated hydrocarbons, *Chemosphere*, 16, 1949, 1987.
152. Isosaari, P., Kohonen, T., Kiviranta, H., Tuomisto, J., and Vartiainen, T., Assessment of levels, distribution, and risks of polychorinated dibenzo-*p*-dioxins and dibenzofurans in the vicinity of a vinyl chloride production plant, *Environ. Sci. Technol.*, 34, 2684, 2000.
153. Olie, K., Vermuelen, P. L., and Hutzinger, O., Chlorodibenzo-*p*-dioxins and chlorodibenzofurans are trace components of fly ash and flue gas of some municipal incinerators in the Netherlands, *Chemosphere*, 8, 455, 1977.

154. Dow Chemical Co., The Trace Chemistries of Fire — A source of and Routes for the Entry of Chlorinated Dioxins into the Environment, Dow Chemical Company, Midland, MI, 1978.
155. Smith, R. M., O'Keefe, P. W., Hilker, D. R., and Aldous, K. M., Ambient air and incinerator testing for chlorinated dibenzofurans and dioxins by low resolution mass spectrometry, *Chemosphere*, 18, 585, 1989.
156. Siebert, P. C., Alston-Guiden, D., and Jones, K. H., An analysis of worldwide resource recovery emissions and the implications for risk assessment, in *Health Effects of Municipal Waste Incineration*, Hattemer-Frey, H. A. and Travis, C., Eds., CRC Press, Boca Raton, FL, 1991, Chap. 1.
157. W.H.O., PCDD and PCDF Emissions from Incineration, Environmental Health 17, WHO/EURO Copenhagen, Denmark, 1987.
158. Rappe, C. and Buser, H.-R., Chemical and physical properties, analytical methods, sources and environmental levels of halogenated dibenzodioxins and dibenzofurans, in *Halogenated Biphenyls, Triphenyls, Naphthalenes, Dibenzodioxins and Related Compounds*, Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 1989, Chap. 3.
159. Shin, D. H., Choi, S. M., Oh, J. E., and Chang, Y. S., Evaluation of polychlorinated dibenzo-*p*-dioxin/dibenzofuran (PCDD/PCDF) emissions in municipal solid waste incinerators, *Environ. Sci. Technol.*, 33, 2657, 1999.
160. Brown, R. S., Pettit, K., Mundy, K. J., Jones, P. W., and Noble, W., Incineration: The British experience, *Chemosphere*, 20, 1785, 1990.
161. Lindner, G., Jenkins, A. C., McCormack, J., and Adrian, R. C., Dioxins and furans from medical waste incinerators, *Chemosphere*, 20, 1793, 1990.
162. Manscher, O. H., Heidam, N. Z., Vikelsoe, J., Nielsen, P., Blinksbjerg, P., Madsen, H., Pallesen, L., and Tiernan, T. O., The Danish incinerator dioxin study. Part 1, *Chemosphere*, 20, 1779, 1990.
163. Hagenmaier, M., Kraft, M., Brunner, H., and Haag, R., Catalytic effects of fly ash from waste incineration facilities on the formation and decomposition of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans, *Environ. Sci. Technol.*, 21, 1080, 1987.
164. Rappe, C., Sources of Exposure, Environmental Levels and Exposure Assessment of PCDDs and PCDFs, Extended Abstracts, Vol. 9, p 5, *12th Int. Symp. Dioxins Related Compd.*, Tampere, Finland, 1992.
165. Tysklind, M., Söderstrom, G., and Rappe, C., PCDD and PCDF emissions from scrap metal melting processes at a steel mill, *Chemosphere*, 19, 705, 1989.
166. Harnly, M., Stephens, R., McLaughlin, C., Marcotte, J., Petreas, M., and Goldman, L., Polychlorinated dibenzo-*p*-dioxin and dibenzofuran contamination at metal recovery facilities, open fire sites, and a railroad car incineration facility, *Environ. Sci. Technol.*, 29, 677, 1995.
167. Marklund, S., Rappe, C., Tysklind, M., and Egeback, K-E., Identification of polychlorinated dibenzofurans and dioxins in exhausts from cars run on leaded gasoline, *Chemosphere*, 16, 29, 1987.
168. Bingham, A. G., Edmunds, C. J., Graham, B. W. L., and Jones, M. T., Determination of PCDDs and PCDFs in car exhaust, *Chemosphere*, 19, 669, 1989.
169. Geueke, K. J., Gessner, A., Quass, U., Broker, G., and Hiester, E., PCDD/PCDF emissions from heavy duty vehicle diesel engines, *Chemosphere*, 38, 2791, 1999.
170. Ryan, J. V. and Gullett, B. K., On-road emission sampling of heavy-duty diesel trucks for polychlorinated dibenzo-*p*-dioxins and dibenzofurans, *Environ. Sci. Technol.*, 34, 4483, 2000.
171. Lamieux, P. M., Lutes, C. C., Abbott, J. A., and Aldous, K. M., Emissions of polychlorinated dibenzo-*p*-dioxins polychlorinated dibenzofurans from the open burning of household waste in barrels, *Environ. Sci. Technol.*, 34, 377, 2000.
172. Lee, R. G. M., Green, N. J. L., Lohmann, R., and Jones, K. C., Seasonal, anthropogenic, air mass and meterolological influences on the atmospheric concentrations of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDDs/PCDFs): Evidence for the importance of diffuse combustion sources, *Environ. Sci. Technol.*, 33, 2864, 1999.
173. Cook, P. M., Batterman, A. R., Butterworth, B. C., and Lodge, K. B., Laboratory Study of TCDD Bioaccumulation by Lake Trout from Lake Ontario Sediments, Food Chain and Water, in *Lake Ontario TCDD Bioaccumulation Study Final Report*, U.S. Environmental Protection Agency, New York, 1990, Chap. 6.
174. Loonen, H., Tonkes, M., Parsons, J. R., and Govers, H. A. J., Relative contributions of water and food to the bioaccumulation of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans in guppies, *Sci. Total Environ.*, Suppl. 491, 1993.

175. Loonen, H., Parsons, D., Govers, H. A. J., Effect of sediment on the bioaccumulation of a complex mixture of polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) by fish, *Chemosphere*, 28, 1433, 1994.
176. Kuehl, D. W., Cook, P. M., Batterman, A. R., Lothenbach, D., and Butterworth, B. C., Bioavailability of polychlorinated dibenzo-*p*-dioxins and dibenzofurans from contaminated Wisconsin River sediment to carp, *Chemosphere*, 16, 667, 1987.
177. Rubinstein, N. I., Pruell, R. J., Taplin, B. K., Li Volsi, J. A., and Norwood, C. B., Bioavailability of 2,3,7,8-TCDD, 2,3,7,8-TCDF and PCBs to marine benthos from Passaic River sediments, *Chemosphere*, 20, 1097, 1990.
178. Fairchild, W. L., Muir, D. C. G., Currie, R. S., and Yarechewski, A. L., Emerging insects as a biotic pathway for movement of 2,3,7,8-tetrachlorodibenzofuran from lake sediments, *Environ. Toxicol. Chem.*, 11, 867, 1992.
179. Kuehl, D. W., Cook, P. M., Batterman, A. R., Lothenbach, D. B., Butterworth, B. C., and Johnson, D. L., Bioavailability of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin from municipal incinerator flyash to freshwater fish, *Chemosphere*, 14, 427, 1985.
180. Kuehl, D. W., Cook, P. M., Batterman, A. R., and Butterworth, B. C., Isomer dependent bioavailability of polychlorinated dibenzo-*p*-dioxins and dibenzofurans from municipal incinerator flyash to carp, *Chemosphere*, 16, 657, 1987.
181. Van den Berg, M., Blank, F., Heeremans, C., Wagenaar, H., and Olie, K., Presence of polychlorinated dibenzo-*p*-dioxins and dibenzofurans in fish-eating birds and fish from the Netherlands, *Arch. Environ. Contam. Toxicol.*, 16, 149, 1987.
182. Braune, B. M. and Norstrom, R. J., Dynamics of organochlorine compounds in herring gulls: III. Tissue distribution and bioaccumulation in Lake Ontario gulls, *Environ. Toxicol. Chem.*, 8, 957, 1989.
183. Kuroki, J., Koga, N., and Yoshimura, H., High affinity of 2,3,4,7,8-pentachloro-dibenzofuran to cytochrome P-450 in hepatic microsomes of rats, *Chemosphere*, 15, 731, 1986.
184. Pastor, D., Ruiz, X., Barcelo, D., and Albaiges, J., Dioxins, furans and AHH-active PCB congeners in eggs of two gull species from the Western Mediterranean, *Chemosphere*, 31, 3397, 1995.
185. Fanelli, R., Bertoni, M. P., Bonfanti, M., Castelli, M. G., Chiabrando, C., Martelli, G. P., N'e, M.A., Noseda, A., and Sbarra, C., Routine analysis of 2,3,7,8-tetrachlorodi-benzo-*p*-dioxin in biological samples from the contaminated area of Seveso, Italy, *Bull. Environ. Contam. Toxicol.*, 24, 818, 1980.
186. Chang, R., Hayward, D., Goldman, L., Hanly, M., Flattery, J., and Stephens, R., Foraging farm animals as biomonitors for dioxin contamination, *Chemosphere*, 19, 481, 1989.
187. Stephens, R. D., Petreas, M. X., and Haywood, D. G., Biotransfer and bioaccumulation of dioxins and dibenzofurans from soil, extended abstracts, Vol. 8, p 377, 12th *Int. Symp. Dioxins Related Compds.*, Tampere, Finland, 1992.
188. McConnell, E. E., Lucier, G. W., Rumbaugh, R. C., Albro, P. W., Harvan, D. J., Hass, J. R., and Harris, M. W., Dioxin in soil: Bioavailability after ingestion by guinea pigs, *Science*, 223, 1077, 1984.
189. Umbeit, T. H., Hesse, E. J., and Gallo, M. A., Bioavailability of dioxin in soil from a 2,4,5-T manufacturing site, *Science*, 232, 417, 1986.
190. Jensen, D. J., Hummel, R. A., Mahle, N. H., Kocher, C. W., and Higgins, H. S., A residue study on beef cattle consuming 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *J. Agric. Food Chem.*, 29, 265, 1981.
191. McLachlan, M. and Richter, W., Uptake and transfer of PCDDs/PCDFs by cattle fed naturally contaminated feedstuffs and feed contaminated as a result of sewage sludge application. 1. Lactating cows, *J. Agric. Food Chem.*, 46, 1166, 1998.
192. Czuczwa, J. and Hites, R. A., Airborne dioxins and dibenzofurans: Sources and fates, *Environ. Sci. Technol.*, 20, 195, 1986.
193. Pearson, R., Swackhamer, D. L., Eisenreich, S. J., and Long, D. T., Concentrations, accumulations and inventories of polychlorinated dibenzo-*p*-dioxins and dibenzofurans in sediments of the Great Lakes, *Environ. Sci. Technol.*, 31, 2903, 1997.
194. Baker, J. I. and Hites, R. A., Siskiwit revisited: Time trends of polychlorinated dibenzo-*p*-dioxin and dibenzofuran deposition at Isle Royale, Michigan, *Environ. Sci. Technol.*, 34, 2887, 2000.
195. Smith, R. M., O'Keefe, P. W., Aldous, K., Briggs, R., Hilker, D., and Connor, S., Measurement of PCDFs and PCDDs in air samples and lake sediments in upstate New York, *Proc. 11th Int. Symp. Dioxins Related Compd.*, Research Triangle Park, Raleigh, NC, 1991.

196. Rose, C. L., Rose, N. L., Harlock, S., and Fernandes, A., A historical record of polychlorinated dibenzo-*p*-dioxin (PCDD) and polychlorinated dibenzofuran (PCDF) deposition to a remote lake site in north-west Scotland, U.K., *Sci. Total Environ.*, 198, 161, 1997.
197. Vartiainen, T., Mannio, J., Korhonen, M., Kinnunen, K., and Strandman, T., Levels of PCDD, PCDF and PCB dated sediments in subartic Finland, *Chemosphere*, 34, 1341, 1997.
198. Juttner, I., Henkelmann, B., Schramm, K. W., Steinberg, C. E. W., Winkler, R., and Kettrrup, A., Occurrence of PCDD/PCDF in dated lake sediments of the Black Forest, Southwestern Germany, *Environ. Sci. Technol.*, 31, 806, 1997.
199. Bruzy, L. P. and Hites, R. A., Global mass balance for polychlorinated dibenzo-*p*-dioxins and dibenzofurans, *Environ. Sci. Technol.*, 30, 1797, 1996.
200. Baker, J. I. and Hites, R. A., Polychlorinated dibenzo-*p*-dioxins and dibenzofurans in the remote North Atlantic marine atmosphere, *Environ. Sci. Technol.*, 33, 14, 1999.
201. Wagrowski, D. M. and Hites, R. A., Insights into the global distribution of polychlorinated dibenzo-*p*-dioxins and dibenzofurans, *Environ. Sci. Technol.*, 34, 2952, 2000.
202. Baker, J. I. And Hites, R. A., Is combustion the major source of polychlorinated dibenzo-*p*-dioxins and dibenzofurans in the environment? A mass balance investigation, *Environ. Sci. Technol.*, 34, 2879, 2000.
203. Tyler, A. O., Millward, G. E., Jones, P. H., and Turner, A., Dioxins in U.K. Estuaries, Extended Abstracts, *12th Int. Symp. Dioxins Related Compd.*, Tampere, Finland, 9, 295, 1992.
204. Dung, M. H. and O'Keefe, P. W., Comparative rates of photolysis of polychlorinated dibenzofurans in organic solvents and in aqueous solutions, *Environ. Sci. Technol.*, 28, 549, 1994.
205. Kim, M. and O'Keefe, P. W., Photodegradation of polychlorinated dibenzo-*p*-dioxins and dibenzofurans in aqueous solutions and in organic solvents, *Chemosphere*, 41, 793, 2000.
206. Adriaens, P., Fu, Q. Z., and Grbicgalic, D., Bioavailability and transformation of highly chlorinated dibenzo-*p*-dioxins in anaerobic soils and sediments, *Environ. Sci. Technol.*, 29, 2252, 1995.
207. Ballerstedt, H., Krauss, A., and Lechner, U., Reductive dechlorination of 1,2,3,4-tetrachlorodibenzo-*p*-dioxin and its products by anaerobic mixed cultures from Saale River sediment, *Environ. Sci. Technol.*, 31, 1749, 1997.
208. Barkovskii, A. L. and Adriaens, P., Microbial dechlorination of historically present and freshly spiked chlorinated dioxins and diversity of dioxin-dechlorinating populations, *Appl. Environ. Microbiol.*, 62, 4556, 1996.
209. Adriaens, P., Chang, P. R., and Barkovskii, A. L., Dechlorination of PCDD/PCDF by organic and inorganic electron transfer molecules in reduced environments, *Chemosphere*, 32, 433, 1996.
210. Barkovskii, A. L. and Adriaens, P., Impact of humic constituents on microbial dechlorination of polychorinated dioxins, *Environ. Toxicol. Chem.* 17, 1013, 1998.
211. Albrecht, I. D., Barkovskii, A. L., and Adriaens, P., Production and dechlorination of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in historically-contaminated estuarine sediments, *Environ. Sci. Technol.*, 33, 737, 1999.
212. Jensen, S., The PCB Story, *Ambio* 1, 123, 1972.
213. http://www.nwfsc.noaa.gov/issues/Pdfs/EC6504.pdf, National Marine Mammal Contaminant Monitoring, Research Issue Paper, EC 6504 (HQ ID 284/285/286).
214. O'Connor, T. P., *Recent Trends in Coastal Environmental Quality: Results from the First Five Years of the NOAA Mussel Watch Project*, U.S. Printing Office, U.S. Department of Commerce, National Oceanic and Atmospheric Administration, 1992.
215. Bignert, A., Olsson, M., Persson, W., Jensen, S., Zakrisson, S., Litzen, K., Eriksson, U., Haggberg, L., and Alsberg, T., Temporal trends of organochlorines in northern Europe, 1967–1995, Relation to global fractionation, leakage from sediments and international measures, *Environ. Pollut.*, 99, 177, 1998.
216. Muir, D. C. and Norstrom, R. J., Geographical differences and time trends of persistent organic pollutants in the Arctic, *Toxicol. Lett.*, 112–113, 93, 2000.
217. Morrison, H. A., Whittle, M. D., and Haffner, D. G., The relative importance of species invasions and sediment disturbance in regulating chemical dynamics in western Lake Erie, *Ecol. Modeling*, 125, 279, 2000.
218. Bopp, R., Simpson, H. J., Olsen, C. R., Trier, R. M., and Kostyk, N., Chlorinated hydrocarbons and radionuclide chromologies in sediments of the Hudson River estuary, New York, *Environ. Sci. Technol.*, 16, 666, 1982.

219. Golden, K. A., Wong, C. S., Jeremiason, J. D., Eisenreich, S. J., Sanders, G., Hallgren, J., Swackhamer, D. L., Engstrom, D. R., and Long, D. T., Accumulation and preliminary inventory of organochlorines in Great Lakes sediments, *Water Sci. Technol.*, 28, 19, 1993.
220. Broman, D., Naf, C., Axelman, J., and Petersen, H., Time trend analysis of PAHs and PCBs in the northern Baltic proper, *Chemosphere*, 29, 1325, 1994.
221. Scrimshae, M. D. and Lester, J. N., Estimates of the inputs of polychlorinated biphenyls and organochlorine insecticides to the River Thames derived from the sediment record, *Philos. Trans. R. Soc. London, Ser. A*, 355, 189, 1997.
222. Alcock, R. E., Johnston, A. E., McGrath, S. P., Berrow, M. L., and Jone, K. C., Long-term changes in the polychlorinated biphenyl content of United Kingdom soils, *Environ. Sci. Technol.*, 27, 1918, 1993.
223. Jones, K. C., Duarte, D. R., and Cawse, P. A., Changes in the PCB Concentration of United Kingdom air between 1972 and 1992, *Environ. Sci. Technol.*, 29, 272, 1995.
224. Hillery, B. R., Simcik, M., Basu, I., Hoff, R. M., Strachan, W. M. J., Burniston, D., Chan, C. H., Brice, K. A., Sweet, C. W., and Hites, R. A., Atmospheric deposition of toxic pollutants to the Great Lakes as measured by the integrated atmospheric deposition network, *Environ. Sci. Technol.*, 32, 2216, 1998.
225. Simcik, M., Basu, I., Sweet, C. W., and Hites, R. A., Temperature dependence and temporal trends of polychlorinated biphenyl congeners in the Great Lakes atmosphere, *Environ. Sci. Technol.*, 33, 1991, 1999.
226. Hillery, B. R., Basu, I., Sweet, C. W., and Hites, R. A., Temporal and spatial trends in a long-term study of gas-phase PCB concentrations near the Great Lakes, *Environ. Sci. Technol.*, 31, 1811, 1997.
227. O'Keefe, P., Meyer, C., Hilker, D., Aldous, K., Jelus-Tyror, B., Dillon, K., and Donnelly, R., Analysis of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Great Lakes fish, *Chemosphere*, 12, 325, 1983.
228. Ryan, J. J., Lau, P-Y., Pillon, J. C., Lewis, D., McLeod, H. A., and Gervais, A., Incidence and levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in Lake Ontario commercial fish, *Environ. Sci. Technol.*, 18, 719, 1984.
229. Fehringer, N. V., Walters, S. M., Kozara, R. J., and Schneider, L., Survey of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in fish from the Great Lakes and selected Michigan rivers, *J. Agric. Food Chem.*, 33, 626, 1985.
230. Harless, R. L., Oswald, E. O., Lewis, R. G., Dupuy, A. E., Jr., McDaniel, D. D., and Tai, H., Determination of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in fresh water fish, *Chemosphere*, 11, 193, 1982.
231. Norstrom, R. J., Hallett, D. J., Simon, M., and Mulvihill, M. J., Analysis of Great Lakes herring gull eggs for tetrachlorodibenzo-*p*-dioxins, in *Chlorinated Dioxins and Related Compounds: Impact on the Environment*, Hutzinger, O., Frei, R. W., Merian, E., and Pochiari, F., Eds., Pergamon Press, Oxford, 1982, 173.
232. Stalling, D. L., Smith, L. M., Petty, J. D., Hogan, J. W., Johnson, J. L., Rappe, C., and Buser, H. R., Residues of polychlorinated dibenzo-*p*-dioxins and dibenzofurans in Laurentian Great Lakes fish, in *Human and Environmental Risks of Chlorinated Dioxins and Related Compounds*, Tucker, R. E., Young, A. L., and Gray, A. P., Eds., Plenum Publishers, New York, 1983, 221.
233. Zacharewski, T., Safe, L., Safe, S., Chittim, B., DeVault, D., Wiberg, K., Bergqvist, P-E., and Rappe, C., Comparative analysis of polychlorinated dibenzo-*p*-dioxin and dibenzofuran in Great Lakes fish extracts by gas chromatography-mass spectrometry and *in vitro* enzyme induction activities, *Environ. Sci. Technol.*, 23, 730, 1981.
234. Kubiak, T. J., Harris, H. J., Smith, L. M., Schwartz, T. R., Stalling, D. I., Trick, J. A., Sileo, L., Docherty, D. E., and Erdman, T. C., Microcontaminants and reproductive impairment of the Forster's tern on Green Bay, Lake Michigan — 1983, *Arch. Environ. Contam. Toxicol.*, 18, 706, 1989.
235. Korfmacher, W. A., Hansen, E. B., Jr., and Rowland, K. L., Tissue distribution of 2,3,7,8-TCDD in bull frogs obtained from a 2,3,7,8-TCDD contaminated area, *Chemosphere*, 15, 121, 1986.
236. Ryan, J. J., Lau, B. P-Y., Hardy, J. A., Stone, W. B., O'Keefe, P., and Gierthy, J., 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and related dioxins and furans from snapping turtle tissues (Chelydra serpentina) from the Upper St. Lawrence River, *Chemosphere*, 15, 537, 1986.
237. Rappe, C., Bergqvist, P-E., Kjeller, L-O., Swanson, S., Belton, T., Ruppel, B., Lockwood, K., and Kahn, P. C., Levels and patterns of PCDD and PCDF contamination in fish, crabs and lobsters from Newark Bay and New York Bight, *Chemosphere*, 22, 239, 1991.

238. Gotz, R., Schumacher, E., Kjeller, L-O., Bergqvist, P-A., and Rappe, C., Polychlorierte Dibenzo-*p*-Dioxine (PCDDs) und Polychlorierte Dibenzofurane (PCDFs) in Sedimenten und Fischen aus dem Hamburger Hafen, *Chemosphere*, 20, 51, 1990.
239. Luckas, B. and Oehme, M., Characteristic contamination levels for polychlorinated hydrocarbons, dibenzofurans and dibenzo-*p*-dioxins in bream (*Abramis brama*) from the River Elbe, *Chemosphere*, 21, 79, 1990.
240. Frommberger, R., Polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans in fish from South-West Germany: River Rhine and Neckar, *Chemosphere*, 22, 29, 1991.
241. Rappe, C., Bergqvist, P.-A., and Kjeller, L-O., Levels, trends and patterns of PCDDs and PCDFs in Scandinavian environmental samples, *Chemosphere*, 18, 651, 1989.
242. Hebert, C. E., Norstrom, R. J., Simon, M., and Braune, B. M., Temporal trends and sources of PCDDs and PCDFs in the Great Lakes: Herring gull monitoring, 1981–1991, *Environ. Sci. Technol.*, 28, 1268, 1994.
243. Firestone, D., Fehringer, N. V., Walters, S. M., Kozan, R. J., Ayres, R. J., Ogger, J., Schneider, L., Glidden, R. M., Ahlrep, J. R., Brown, P. J., Ford, S. E., Davy, R. A., Gulick, D. J., McCullough, B. H., Sittig, R. A., Smith, P. V., Syvertson, C. N., and Barber, M. R., TCDD residues in fish and shellfish from US waterways, *J. AOAC Int.*, 79, 1174, 1996.
244. Elliott, J. E. and Norstrom, R. J., Chlorinated hydrocarbon contaminants and productivity of Bald Eagle populations on the Pacific coast of Canada, *Environ. Toxicol. Chem.*, 17(6), 1142–1153, 1998.
245. Ling, Y., Soong, D. K., and Lee, M. K., PCDD/PCDFs and coplanar PCBs in sediment and fish samples from the Er-Jen River in Taiwan, *Chemosphere*, 31, 2863, 1995.
246. Tarasova, E. N., Mamontov, A. A., Mamontova, E. A., Klasmeier, J., and McLachlan, M. S., Polychorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) in Baikal seal, *Chemosphere*, 34, 2419, 1997.
247. Norwood, C. B., Hackett, M., Pruell, R. J., Butterworth, B. C., Williamson, K. J., and Nauman, S. M., Polychlorinated dibenzo-*p*-dioxins and dibenzofurans in selected estuarine sediments, *Chemosphere*, 18, 553, 1989.
248. Creaser, C. S., Fernandes, A. R., Al-Haddad, A., Harrad, S. J., Homer, R. B., Skett, P. W., and Cox, E. A., Survey of background levels of PCDDs and PCDFs in U.K. soils, *Chemosphere*, 18, 767, 1987.
249. Creaser, C. S., Fernandes, A. R., Harrad, S. J., and Cox, E. A., Levels and sources of PCDDs and PCDFs in urban British soils, *Chemosphere*, 21, 931, 1990.
250. Rotard, W., Christmann, W., and Knoth, W., Background levels of PCDD/PCDF in soils in Germany, *Chemosphere*, 29, 2193, 1994.
251. Horstman, M., Bopp, U., and McLachlan, M. S., Comparison of the bulk deposition of PCDD/PCDF in a spruces forest and an adjacent clearing, *Chemosphere*, 34, 1245, 1997.
252. Eitzer, B. D. and Hites, R. A., Atmospheric transport and deposition of polychlorinated dibenzo-*p*-dioxins and dibenzofurans, *Environ. Sci. Technol.*, 23, 1396, 1984.
253. Lohmann, R., Green, N. J. L., and Jones, K. C., Atmospheric transport of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDDs/PCDFs) in air masses across the United Kingdom and Ireland: Evidence of emissions and depletion, *Environ. Sci. Technol.*, 33, 2872, 1999.
254. Hiester, E., Bruckman, P., Bohm, R., Eynck, P., Gerlach, A., Mulder, W., Ristow, H., Pronounced decrease of PCDD/PCDF in ambient air, *Chemosphere*, 34, 1231, 1997.
255. Scheuplein, R. J., Gallo, M. A., van der Heijden, K. A., in *Branbury Report 35: Biological Basis for Risk Assessment of Dioxins and Related Compounds (Epilogue)*, Cold Spring Harbor Laboratory Press, Plainview, NY, 1991, 489.
256. Cook, P. M., Erickson, R. J., Spehar, R. L., Bradbury, S. P., and Ankley, G. T., Interim report on data and methods for assessment of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin risks to aquatic life and associated wildlife, EPA/600/R-93/055, Environmental Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, 1993.
257. Van den Berg, M., Birnbaum, L., Bosveld, A. T. C., Brunstrom, B., Cook, P., Feeley, M., Giesy, J. P., Hanberg, A., Hasegawa, R., Kennedy, S. W., Kubiak, T., Larsen, J. C, van Leeuwen, X., Liem, A. K., Nolt, C., Peterson, R. E., Poellinger, L., Safe, S., Schrenk, D., Tillitt, D., Tysklind, M., Younes, M., Waern, F., and Zacharewski, T., Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife, *Environ. Health Perspect.*, 106, 775, 1998.

258. Ahlborg, U. G., Brouwer, A., Fingerhut, M. A., Jacobson, J. L., Jacobson, S. W., Kennedy, S. W., Kettrup, A. A., Koeman, J. H., Poiger, H., Rappe, C., Safe, S. H., Seegal, R., Tuomisto, J., and van den Berg, M., Impact of polychlorinated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls on human and environmental health, with special emphasis on application of the toxic equivalency factor concept, *Eur. J. Pharmacol. Environ. Toxicol. Pharmacol. Sect.*, 228, 179, 1992.
259. Ahlborg, U. G., Becking, G. C., Birnbaum, L. S., Brouwer, A., Derks, H. J. G. M., Feeley, M., Golor, G., Hanberg, A., Larsen, J. C., Liem, A. K. D., Safe, S. H., Schlatter, C., Younes, M., and Yrjanheikki, E., Toxic equivalency factors for dioxin-like PCBs. Chemosphere, 28, 1049, 1994.
260. U.S. Fish and Wildlife website, http://njfieldoffice.fws.gov/Contaminants/Contaminants.htm
261. McFarland, V. A. and Clarke, J. U., Environmental occurrence, abundance and potential toxicity of polychlorinated biphenyl congeners: Considerations for a congener-specific analysis, *Environ. Health Perspect.*, 81, 225, 1989.
262. Tillitt, D. E., Gale, R. W., Meadows, J. C., Zajicek, J. L., Peterman, P. H., Heaton, S. N., Jones, P. D., Bursian, S. J., Kubiak, T. J., Giesy, J. P., and Aulerich, R. J., Dietary exposure of mink to carp from Saginaw Bay. 3. Characterization of dietary exposure to planar halogenated hydrocarbons, dioxin equivalents, and biomagnification, *Environ. Sci. Technol.*, 30, 283, 1996
263. Liem, A. K. D., Furst, P., and Rappe, C., Exposure of populations to dioxins and related compounds, *Food Additives Contam.*, 17, 241, 2000.
264. Verrett, M. J., Investigation of the Toxic and Teratogenic Effects of Halogenated Dibenzo-*p*-dioxins and Dibenzofurans in the Developing Chicken Embryo, Memorandum Report, U.S. Food and Drug Administration, Washington, D.C., 1976.
265. Goldstein, J. A., Structure-activity relationships for the biochemical effects and the relationship to toxicity, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds*, Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 1980, Chap. 6.
266. Giesy, J. P. and Kannan, K., Dioxin-like and non-dioxin-like toxic effects of polychlorinated biphenyls (PCBs): Implications for risk assessment, *Crit. Rev. Toxicol.*, 28, 511, 1998.
267. Bergman, A., Athanasiadou, M., Bergek, S., Haraguchi, Jensen, S., and Klasson-Wehler, E., PCB and PCB methyl sulfones in mink treated with PCBs and various PCB fractions, *Ambio*, 21, 570, 1992.
268. Bergman, A., Klasson-Wehler, E., and Kuroki, H., Selective retention of hydroxylated PCB metabolites in blood, *Environ. Health Perspect.* 102, 465, 1994.
269. Porterfield, S. P., Vulnerability of the developing brain to thyroid abnormalities: Environmental insults to the thyroid system, *Environ. Health Perspect.*, 102, Suppl. 2, 125, 1994.
270. Birnbaum, L. S., Endocrine effects of prenatal exposure to PCBs, dioxins and other xenobiotics: Implications for policy and future research, *Environ. Health Perspect.*, 102, 767, 1994.
271. World Health Organization (WHO), Consultation on assessment of the health risk of dioxins: Re-evaluation of the tolerable daily intake (TDI): Executive Summary, *Food Additives Contam.*,17, 223, 2000.
272. Tillitt, D. E., The toxic equivalents approach for fish and wildlife, *Hum. Ecol. Risk Assess.*, 5, 25, 1999.
273. Hansen, L. G., *The Ortho side of PCBs: Occurrence and Disposition*, Kluwer, Boston, 1999.
274. Robertson, L. W. and Hansen, L. G., *PCBs — Recent Advances in the Environmental Toxicology and Health Effects*, University of Kentucky Press, Lexington, 2001.
275. Schwetz, B. A., Norris, J. M., Sparschu, G. L., Rowe, V. K., Gehring, P. J., Emerson, J. L., and Gerbig, P. J., Toxicology of chlorinated dibenzo-*p*-dioxins, *Environ. Health Perspect.*, 5, 87, 1973.
276. Poland, A. and Knutson, J. C., 2,3,7,8-tetrachorodibenzo-*p*-dioxin and related halogenated aromatic hydrocarbons: Examination of the mechanism of toxicity, *Ann. Rev. Pharmacol. Toxicol.*, 22, 517, 1982.
277. Safe, S., Polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: Environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs), *CRC Crit. Rev. Toxicol.*, 21, 51, 1990.
278. Greig, J. B., Jones, G., Butler, W. H., and Barnes, J. M., Toxic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Food Cosmet. Toxicol.*, 11, 585, 1973.
279. Heath, R. G., Spann, J. W., Kreitzer, J., and Vance, C., Effects of polychlorinated biphenyls on birds. in *Proc. XV^TH Int. Ornithol. Congr.*, Voous, K. H., Ed., The Hague, The Netherlands, 1972, 475.
280. Hochstein, J. R., Aulerlich, R. J., and Bursian, S. J., Acute toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin to mink, *Arch. Environ. Contam. Toxicol.*, 17, 33, 1988.

281. Vos, J. G., Moore, J. A., and Zinkl, J. G., Toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in C57B1/6 mice, *Toxicol. Appl. Pharmacol.*, 29, 1974, 229.
282. Beatty, P. W., Holscher, M. A., and Neal, R. A., The comparative toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in larval and adult forms of *Rana catesbeina, Bull. Environ. Contam. Toxicol.*, 5, 578, 1976.
283. Olson, J. R., Holscher, M. A., and Neal, R. A., Toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the Golden Syrian hamster, *Toxicol. Appl. Phamarcol.*, 59, 67, 1980.
284. Aulerich, R. J., Bursian, S. J., and Napolitano, A. C., Biological effects of epidermal growth factor and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on developmental parameters of neonatal mink, *Arch. Environ. Contam. Toxicol.*, 17, 1988, 27.
285. Aulerich, R. J., Bursian, S. J., Evans, M. G., Hochstein, J. R., Koudele, K. A., Olson, B. A., and Napolitano, A. C., Toxicity of 3,4,5,3',4',5'-hexachlorobiphenyl to mink, *Arch. Environ. Contam. Toxicol.*, 16, 53, 1987.
286. Birnbaum, L., Re-evaluation of dioxin, Presentation at Great Lakes Water Quality Board 102nd Meeting — Chicago, International Joint Commission, Windsor, Canada, 1993.
287. Birnbaum, L. S. and Tuomisto, J., Non-carcinogenic effects of TCDD in animals, *Food Additives Contam.*, 17, 275, 2000.
288. Powell, D. C., Aulerich, R. J., Meadows, J. C., Tillitt, D. E., Giesy, J. P., Stromborg, K. L., and Bursian, S. J., Effects of 3,3',4,4',5-pentachlorobiphenyl (PCB 126) and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) injected into the yolks of chicken (*Gallus domesticus*) eggs prior to incubation, *Arch. Environ. Contam. Toxicol.*, 31, 404, 1996.
289. Mably, T. A., Moore, R. W., and Peterson, R. E., *In utero* and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. 1. Effects on androgenic status, *Toxicol. Appl. Pharmacol.*, 114, 97, 1992a.
290. Mably, T. A., Moore, R. W., Goy, R. W., and Peterson, R. E., *In utero* and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. 2. Effects on sexual behavior and the regulation of luteinizing hormone secretion in adulthood, *Toxicol. Appl. Pharmacol.*, 114, 108, 1992b.
291. Mably, T. A., Bjerke, D. L., Moore, R. W., Gendron-Fitzpatrick, A., and Petterson, R. E., *In utero* and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin: 3. Effects on spermatogenesis and reproductive capability, *Toxicol. Appl. Pharmacol.*, 114, 118, 1992c.
292. Gray, L. E., Jr. and Ostby, J. S., *In utero* 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) alters reproductive morphology and function in female rat offspring, *Toxicol. Appl. Pharmacol.*, 133, 285, 1995.
293. Gray, L. E., Jr., Kelce, W. R., Monosson, E., Ostby, J. S., and Birnbaum, L. S., Exposure to TCDD during development permanently alters reproductive function in male Long Evans rats and hamsters: Reduced ejaculated and epididymal sperm numbers and sex accessory gland weights in offspring with normal androgenic status, *Toxicol. Appl. Pharmacol.*, 131, 108, 1995.
294. Gray, L. E., Jr., Ostby, J. S., and Kelce, W. R., A dose-response analysis of the reproductive effects of a single gestational dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in male Long Evans hooded rat offspring, *Toxicol. Appl. Pharmacol.*, 146, 11, 1997a.
295. Gray, L. E., Jr., Wolf, C., Mann, P., and Ostby, J. S., *In utero* exposure to low doses of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin alters reproductive development of female Long Evans hooded rat offspring, *Toxicol. Appl. Pharmacol.*, 146, 237, 1997b.
296. Safe, S., Metabolism, uptake, storage and bioaccumulation, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products,* Kimbrough, R. D. Ed., Elsevier/North-Holland Biomedical Press, New York, 1980, 81.
297. Safe, S., Polyhalogenated aromatics: Uptake, disposition and metabolism, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products,* Kimbrough, R. D. and Jensen, A. A., Eds., 2nd ed., Elsevier, Amsterdam, New York, Oxford, 1989, 131.
298. Sawyer, T. and Safe, S., PCB isomers and congeners: Induction of arylhydrocarbon hydroxylase and ethoxyresorufin o-deethylase enzyme activities in rat hepatoma cells, *Toxicol. Lett.*, 13, 57, 1982.
299. Goldstein, J. A. and Safe, S., Mechanism of action and structure-activity relationship for the chlorinated dibenzo-*p*-dioxins and related compounds, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds,* Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 2nd ed., 1989, Chap. 6.
300. Bosveld, A. T. C. (Bart), and van den Berg, M., Effects of polychorinated biphenyls, dibenzo-*p*-dioxins and dibenzofurans on fish-eating birds, *Environ. Rev.*, 2, 147, 1994.

301. Whyte, J. J., Jung, R. E., Schmitt, C. J., and Tillitt, D. E., Ethoxyresorufin-*O*-deethylase (EROD) activity in fish as a biomarker of chemical exposure, *Crit. Rev. Toxicol.*, 30, 347, 2000.
302. Freeman, H. C., Sangalang, G. B., and Fleming, B., The sublethal effects of polychlorinated biphenyl (Aroclor 1254) diet on the Atlantic cod (*Gadus morhua*), *Sci. Total Environ.*, 24, 1, 1982.
303. Klotz, A. V., Stegmann, J. J., and Walsh, C., An aryl hydrocarbon hydroxylating hepatic cytochrome P-450 from the marine fish *Stenotomus chrysops*, *Arch. Biochem. Biophys.*, 226, 578, 1983.
304. Spies, R. B. and Rice, D. W., Effects of organic chemicals on the starry flounder *Platichthys stellatus* in San Francisco Bay. II. Reproductive success of fish captured in San Francisco Bay and spawned in the laboratory, *Mar. Biol.*, 98, 191, 1988.
305. Marcquenski, S. V. and Brown, S. B., Early mortality syndrome in the salmonid fishes from the Great Lakes, in *Chemically Induced Alterations in Functional Development and Reproduction in Fishes*, Rolland, R. M., Gilbertson, M., and Peeterson, R. E., Eds., Society of Environmental Toxicology and Chemistry, Pensacola, FL, 1997, Chap. 10.
306. Kuiken, T., Fox, G. A., and Danesik K. L., Bill malformations in double-crested cormorants with low exposure to organochlorines, *Environ. Toxicol. Chem.*, 18, 2908, 1999.
307. Moccia, R. D., Fox, G. A., and Britton, A., A quantitative assessment of thyroid histopathology of herring gulls (*Larus argentatus*) from the Great Lakes and a hypothesis on the causal role of environmental contaminants, *J. Wildl. Dis.*, 22, 60, 1986
308. Nebeker, A. V. and Puglisi, A., Effect of polychlorinated biphenyls (PCB's) on survival and reproduction of *Daphnia, Gammarus, and Tanytarus*, *Trans. Am. Fish. Soc.*, 103, 722, 1974a.
309. Nebeker, A. V, Puglisi, A., and DeFoe, D. L., Effect of polychlorinated biphenyl compounds on survival and reproduction of the fathead minnows and flagfish, *Trans. Am. Fish. Soc.*, 103, 562, 1974b.
310. Mayer, J., Mehrle, P. M., and Sanders, H. O., Residue dynamics and biological effects of polychlorinated biphenyls in aquatic organisms, *Arch. Environ. Contam. Toxicol.*, 5, 501, 1977.
311. Mayer, K. S., Mayer,.L., and Witt, A., Jr., Waste transformer oil and PCB toxicity to rainbow trout, *Trans. Am. Fish. Soc.*, 114, 869, 1985.
312. Walker, M. K., Spitsbergen, J. M., Olson, J. R., and Peterson, R. E., 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) toxicity during early life stage development of lake trout (*Salvelinus namaycush*), *Can. J. Fish. Aquat. Sci.*, 48, 875, 1991a.
313. Walker, M. K. and Peterson, R. E., Potencies of polychlorinated dibenzo-*p*-dioxin, dibenzofuran, and biphenyl congeners, relative to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, for producing early life stage mortality in rainbow trout (*Oncorhynchus mykiss*), *Aquat. Toxicol.*, 21, 219, 1991b.
314. Kleeman, J. M, Olson, J. R., and Peterson, R. E., Species differences in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxicity and biotransformation in fish, *Fundam. Appl. Toxicol.*, 10, 206, 1988.
315. Hansen, L. G., Wiekhotst, W. B., and Simon, J., Effects of dietary Aroclor 1242 on channel catfish (*Ictalurus punctatus*) and the selective accumulation of PCB components, *J. Fish. Res. Bd. Can.*, 33, 1343, 1976.
316. Elonen, G. E., Spehar, R. L., Holcombe, G. W., Johnson, R. D., Fernandez, J. D., Erickson, R. J., Tietge, J. E., and Cook, P. M., Comparative toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin to seven freshwater fish species during early life-stage development, *Environ. Toxicol. Chem.*, 17, 472, 1998.
317. Tietge, J. E., Johnson, R. D., Jensen, K. M., Cook, P. M., Elonen, G. E., Fernandez, J. D., Holcombe, G. W., Lothenbach, D. B., and Nichols, J. W., Reproductive toxicity and disposition of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in adult brook trout (*Salvelinus fontinalis*) following a dietary exposure, *Environ. Toxicol. Chem.*, 17, 2395, 1998.
318. Johnson, R. D., Tietge, J. E., Jensen, K. M. Fernandez, J. D., Linnum, A. L., Lothenbach, D. B., Holcombe, G. W., Cook, P. M., Christ, S. A., Lattier, D. L., and Gordon, D. A., Toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin to early life stage brook trout (*Salvelinus fontinalis*) following parental dietary exposure, *Environ. Toxicol. Chem.*, 17, 2408, 1998.
319. Walker, M. K. and Peterson, R. E., Toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin to brook trout (*Salvelinus fontinalis*) during early development, *Environ. Toxicol. Chem.*, 13, 817, 1994.
320. Nichols, J. W., Jensen, K. M., Tietge, J. E., and Johnson, R. D., Physiologically based toxicokinetic model for maternal transfer of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in brook trout (*Salvelinus fontinalis*), *Environ. Toxicol. Chem.*, 17, 2442, 1998.
321. Hickey, C. R., Jr. and Young, B. H., Incidence of morphological abnormalities in striped bass from the Hudson River and coastal Long Island, New York, *N.Y. Fish and Game J.*, 31, 104, 1984.

322. Mauck, W. L., Mehrle, P. M., and Mayer, L., Effects of the polychlorinated biphenyl Aroclor 1254 on growth, survival, and bone development in brook trout (*Salvelinus fontinalis*), *J. Fish. Res. Bd. Can.*, 35, 1084, 1978.
323. Cook, P. M. and Burkhard, L. P., Development of bioaccumulation factors for protection of fish and wildlife in the Great Lakes, in *Proc. Natl. Sediment Bioaccumulation Conf.*, U.S. Environmental Protection Agency, EPA 823-R-98–002, 3–19, 1998.
324. Fisher, J. P., Spitsbergen, B. B., Bush, B., and Janhan, P. G., Effect of embryonic PCB exposure on hatching success, survival, growth, and developmental behavior in landlocked Atlantic salmon, *Salmo salar*, in *Environmental Toxicology and Risk Assessment: 2nd Volume*, Gorsuch, J. W., Dwyer, J., Ingersoll, C. G., and LaPoint, T. W., Eds., ASTM Publications, Philadelphia, 298, 1994.
325. Cantrell, S. M., Lutz, L. H., Tillitt, D. E., and Hannink, M., Embryotoxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD): The embryonic vasculature is a physiological target for TCDD-induced DNA damage and apoptotic cell death in medaka (*Orizia latipes*), *Toxicol. Appl. Pharm.*, 141, 23, 1996.
326. Cantrell, S. M., Joy-Schlezinger, J., Stegeman, J. J., Tillitt, D. E., and Hannink, M., Correlation of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-induced apoptotic cell death in the embryonic vasculature with embryotoxicity, *Toxicol. Appl. Pharm.*, 148, 24, 1998.
327. Toomey, B.H., Bello, S., Hahn, M.E., Cantrell, S., Wright, P., Tillitt, D.E., and Di Giulio, R.T., 2,3,7,8-tetrachlorodibenzo-*p*-dioxin induces apoptotic cell death and cytochrome P4501A expression in developing *Fundulus heteroclitus* embryos, *Aquat.Toxicol.*, 51, 127, 2001.
328. Ernst, W., Pesticides and technical organic chemicals, in *Marine Ecology*, Vol. V, Part 4, Kinne, O., Ed., John Wiley and Sons, New York, 1984, 1617.
329. Hendricks, J. D., Putman, T. P., and Sinnhuber, R. O., Null effect of dietary Aroclor 1254 on heptacellular carcinoma incidence in rainbow trout (*Salmo gairdneri*) exposed to aflatoxin B_1 as embryos, *J. Environ. Toxicol. Pathol.*, 4, 9, 1980
330. Leatherland, J. and Sonstegard, R. A., Lowering of serum thyroxine and triiodothyronine levels in yearling coho salmon, (*Oncorhynchus kisutch*) by dietary mirex and PCBs, *J. Fish. Res. Bd. Can.*, 35, 1285, 1978.
331. Anderson, M. J., Miller, M. R., and Hinton, D. E., *In vitro* modulation of 17-beta-estradiol-induced vitellogenin synthesis: Effects of cytochrome P4501A1 inducing compounds on rainbow trout (*Oncorhynchus mykiss*) liver cells, *Aquat. Toxicol.*, 34, 327, 1996.
332. Pesonen, M., Korkalainen, M., Laitinen, J. T., Andersson, T. B., and Vakkuri, O., 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin alters melatonin metabolism in fish hepatocytes, *Chem. Biol. Interact.*, 126, 227, 2000.
333. Schmitt, C. J., Bartish, T. M., Blazer, V. S., Gross, T. S., Tillitt, D. E., Bryant, W. L., and Deweese, L. R., Biomonitoring of environmental status and trends (BEST) program: Contaminants and related effects in fish from the Mississippi, Columbia, and Rio Grande basins, Water-Resour. Invest. Rep. (U.S. Geological Survey), 99–4018B, U.S. Geological Survey Toxic Substances Hydrology Program, 2, 437, 1999.
334. Thomas, P., Effects of Aroclor 1254 and cadmium on reproductive endocrine function and ovarian growth in Atlantic croaker, *Mar. Environ. Res.*, 28, 499, 1989.
335. Khan, I. A. and Thomas, P., Disruption of neuroendocrine function in Atlantic croaker exposed to Aroclor 1254, *Mar. Environ. Res.*, 42, 145, 1996.
336. Khan, I. A. and Thomas, P., Aroclor 1254-induced alteration in hypothalamic monamine metabolism in the Atlantic Croaker (*Micopogonia undulatus*): Correlation with pituitary gonaotropin release, *Neurotoxicology*, 18, 553, 1997.
337. Stouthart, W. J. H. X., Huijbregts, M. A. J., Balm, P. H. M., Lock, R. A. C., and Wendleaar Bonga, S. E., Endocrine stress response and abnormal development in carp (*Cyrinus carpio*) larvae after exposure of the embryos to PCB 126, *Fish Physiol. Biochem.*, 18, 321, 1998.
338. Smeets, J. M. W., van Holsteijn, I., Giesy, J. P., and van den Berg, M., The anti-estrogenicity of Ah receptor agonists in carp (*Cyprinus carpio*) hepatocytes, *Toxicol. Sci.*, 52, 178, 1999.
339. Nirmala, K., Oshima, Y., Lee, R., Imada, N., Honjo, T., and Kobayashi, K., Transgenerational toxicity of tributyltin and its combined effects with polychlorinated biphenyls on reproductive processes in Japanese medaka (*Oryzias latipes*), *Environ. Toxicol. Chem.*, 18, 717, 1999.
340. Olsson, P. E., Westerlund, L., Teh, S. J., Billsson, K., Berg, A. H., Tysklind, M., Nilsson, J., Eriksson, L. O., and Hinton, D. E., Effects of maternal exposure to estrogen and PCB on different life stages of zebrafish (*Danio rerio*), *Ambio*, 28, 100, 1999.

341. Harris, G. E., Kiparissis, Y., and Metcalfe, C. D., Assessment of the toxic potential of PCB congener 81 (3,4,4',5-tetrachlorobiphenyl) to fish in relation to other non-ortho-substituted PCB congeners, *Environ. Toxicol. Chem.*, 13, 1405, 1994.
342. Noguchi, G. E., Immunological disorders associated with polychlorinated biphenyls and related halogenated aromatic compounds, in *Fish Diseases and Disorders Volume 2: Non-Infectious Disorders,* Leatherland, J., and Woo, P. T. K., Eds., CABI, Wallingford, U.K., 1998, Chap. 6.
343. Sijm, T. H. M. and Opperhuizen, A., Dioxins: An environmental risk for fish? in *Environmental Contaminants in Wildlife — Interpreting Tissue Concentrations*, Byer, W. N., Heinz, G. H., and Redmon-Norwood, A. W., Eds., CRC Press, Boca Raton, FL, 1995, Chap. 8.
344. Giesy, J. P. and Snyder, E. M., Xenobiotioc modulation of endocrine responses in fishes, in *Principles and Processes for Evaluating Endocrine Disruption in Wildlife,* Kendall, R., Dickerson, R, Giesy, J., and Suk, W., Eds., Lewis Publishers, Chelsea, MI, 1998, Chap. 8.
345. Fairbrother, A., Ankley, G. T., Birnbaum, L. S., Bradbury, S. P., Francis, B., Gray, L. E., Hinton, D., Johnson, L. L., Peterson, R. E., and van der Kraak, G., Reproductive and developmental toxicology of contaminants in oviparous animals, in *Reproductive and Developmental Effects of Contaminants in Oviparous Vertebrates,* Di Giulio, R. T. and Tillitt, D. E., Eds., SETAC, Pensacola, FL, 1997, Chap. 5.
346. Stegeman, J. J., Schlezinger, J. J., Craddock, J. E., and Tillitt, D. E., Cytochrome P450 1A expression in midwater fishes: Potential of chemical contaminants in remote oceanic zones, *Environ. Sci. Technol.*, 35, 54, 2001.
347. Sileo, L., Karstad, L., Frank, R., Holdrinet, M. V. H., Addison, E., and Braun, H. E., Organochlorine poisoning of ring-billed gulls in southern Ontario, *J. Wildl. Dis.*, 13, 313, 1977.
348. Firestone, D., Etiology of chick edema disease, *Environ. Health Perspect.*, 5, 59, 1973.
349. Heath, R. G., Spann, J. W., Hill, E., and Kreitzer, J., Comparative dietary toxicities of pesticides to birds, U.S. Fish Wildlife Service, Spec. Sci. Rep.-Wildlife, 152, 57, 1972.
350. Dahlgren, R. B., Bury, R. J., Linder, R. L., and Reidinger, R., Jr., Residue levels and histopathology in pheasants given polychlorinated biphenyls, *J. Wildl. Manage.*, 36, 524, 1972.
351. Dahlgren, R. B., Linder, R. L., and Tucker, W. L., Effects of stress on pheasants previously given polychlorinated biphenyls, *J. Wildl. Manage.*, 36, 974, 1972.
352. Vos, J. and Koeman, J., Comparative toxicologic study with polychlorinated biphenyls in chickens with special reference to porphyria, edema formation, liver necrosis, and tissue residues, *Toxicol. Appl. Pharmacol.*, 17, 656, 1970.
353. Vos, J. G., Strik, J. J. T. W. A., van Holsteyn, C. W. M., and Pennings, J. H., Polychlorinated biphenyls as inducers of hepatic porphyria in Japanese quail, with special reference to d-aminolevulinic acid synthetase activity, fluorescence, and residues in the liver, *Toxicol. Appl. Pharmacol.*, 20, 232, 1971.
354. Koeman, J. H., van Velzen-Blad, H. C. W., de Vries, R., and Vos, J. G., Effects of PCB and DDE in cormorants and evaluation of PCB residues from an experimental study, *J. Reprod. Fertil. Suppl.*, 19, 353, 1973.
355. Stickel, W. H., Stickel, L., Dyrland, R. A., and Hughes D. L., Aroclor 1254 residues in birds: Lethal levels and loss rates, *Arch. Environ. Contam. Toxicol.*, 13, 7, 1984.
356. Britton, W. M. and Huston, J. M., Influence of polychlorinated biphenyls in the laying hen, *Poult. Sci.*, 52, 1620, 1973.
357. Sotherland, P. R. and Rahn, H., On the composition of bird eggs, *The Condor,* 89, 48, 1987.
358. Scott, M. L., Effects of PCBs, DDT, and mercury compounds in chickens and Japanese quail, *Fed. Proc.*, 36, 1888, 1977.
359. Blazak, W. and Marcum, J. B., Attempts to induce chromosomal breakage in chicken embryos with Aroclor 1242, *Poult. Sci.*, 54, 310, 1975.
360. Peakall, D. B., Lincer, J. L., and Bloom, S. E., Embryonic mortality and chromosomal alterations caused by Aroclor 1254 in ring doves, *Environ. Health Perspect.*, 1, 103, 1972.
361. Srebocan, V., Pompe-Gotal, J., Brmalj, V., and Plazonic, M., Effect of polychlorinated biphenyls (Aroclor 1254) on liver gluconeogenic enzyme activities in embryonic and growing chickens, *Poult. Sci.*, 56, 732, 1977.
362. Brunstrom, B. and Orberg, J., A method for studying embryotoxicity of lipophilic substances experimentally introduced into hens' eggs, *Ambio*, 11, 209, 1982

363. Rifkind, A. B., Sassa, S., Reyes, J., and Muschick, H., Polychlorinated aromatic hydrocarbon lethality, mixed-function oxidase induction, and uroporphyrinogen decarboxylase inhibition in the chick embryo: Dissociation of dose-response relationships, *Toxicol. Appl. Pharmacol.*, 78, 268, 1985.
364. Hoffman, D. J., Melancon, M. J., Klein, P. N., Eisemann, J. D., and Spann, J. W., Comparative developmental toxicity of planar polychlorinated biphenyl congeners in chickens, american kestrel, and common terns, *Environ. Toxicol. Chem.*, 17, 747, 1998.
365. Brunstrom, B. and Halldin, K., EROD induction by environmental contaminants in avian embryo livers, *Comp. Biochem. Physiol. Part C*, 121, 213, 1998.
366. Gilbertson, M., Effects on fish and wildlife populations, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds*, 2nd ed., Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 1989, Chap. 4.
367. Gilbertson, M., Kubiak T., Ludwig, J., and Fox, G., Great Lakes embryo mortality, edema, and deformities syndrome (GLEMEDS) in colonial fish-eating birds: Similarity to chick-edema disease, *J. Toxicol. Environ. Health*, 33, 455, 1991.
368. Hoffman, D. J., Rice, C. P., and Kubiak, T. J., PCBs and Dioxins in Birds, in *Environmental Contaminants in Wildlife — Interpreting Tissue Concentrations*, Beyer, N. W., Heinz, G. H., and Redmon, A. W., Eds., CRC Press/Lewis Publishers, Boca Raton, FL, 1996a, Chap. 7.
369. Grasman, K. E., Scanlon, P., and Fox, G. A., Reproductive and physiological effects of environmental contaminants in fish-eating birds of the Great Lakes: A review of historic trends, *Environ. Monit. Assess.*, 53, 117, 1998.
370. Clark, K. E., Niles, L. J., and Stansley, W., Environmental contaminants associated with reproductive failure in bald eagle (*Haliaeetus leucocephalus*) eggs in New Jersey, *Bull. Environ. Contam. Toxicol.*, 61, 247, 1998.
371. Schwartz, T. R., Tillitt, D. E., Feltz, K. P., and Peterman, P. H., Determination of mono- and non-o,o'-chlorine substituted polychlorinated biphenyls in aroclors and environmental samples, *Chemosphere*, 26, 1443, 1993.
372. Kubiak, T. J., Personal communication, unpublished data of the Fish and Wildlife Service and U.S. Geological Survey.
373. Bowerman, W. W., Kubiak, T. J., Holt, J.B., Jr., Evans, R. G., Eckstein, R. G., Sindelar, C. R., Best, D. A., and Kozie, K. D., Observed abnormalities in mandibles of nestling bald eagles *Haliaeetus leucocephalus, Bull. Environ. Contam. Toxicol.*, 53, 450, 1994.
374. Hoffman, D. J., Melancon, M. J., Klein, P. N., Rice, C. P., Eisemann, J. D., Hines, R. K., Spann, J. W., and Pendleton, G. W., Developmental toxicity of PCB 126 (3,3',4,4',5-pentachlorobiphenyl) in nestling American kestrels (*Falco sparverius*), *Fundam. Appl. Toxicol.*, 34, 188, 1996b.
375. Summer, C., Giesy, J., Bursian, S., Render, J., Kubiak, T., Jones, P., Verbrugge, D., and Aulerich, R., Effects induced by feeding organochlorine-contaminated carp from Saginaw Bay, Lake Huron, to laying White Leghorn hens. II. Embryotoxic and teratogenic effects, *J. Toxicol. Environ. Health*, 49, 409, 1996.
376. Brunstrom, B., Sensitivity of embryos from duck, goose, herring gull, and various chicken breeds to 3,3',4,4'-tetrachlorobiphenyl, *Poult. Sci.*, 67, 52, 1988.
377. Cecil, H., Bitman, J., Fries, G., Smith, L., and Lillie, R., PCB's in laying hens, American Chemical Society Fall Meeting, 86, 1977.
378. Tumasonis, C., Bush, B., and Baker, D., PCB levels in egg yolks associated with embryonic mortality and deformity of hatched chicks, *Arch. Environ. Contam. Toxicol.*, 1, 312, 1973.
379. Peakall, D. B. and Peakall, M. L., Effects of a polychlorinated biphenyl on the reproduction of artificially and naturally incubated dove eggs, *J. Appl. Ecol.*, 10, 863, 1973.
380. Heinz, G. H., Hill, E., and Contrera, J., Dopamine and norepinephrine depletion in ring doves fed DDE, Dieldrin, and Aroclor 1254, *Toxicol. Appl. Pharmacol.*, 53, 75, 1980.
381. Powell, D. C., Aulerich, R. J., Meadows, J. C., Tillitt, D. E., Powell, J., Restum, J. C., Stromborg, K. L., Giesy, J. P., and Bursian, S. J., Effects of 3,3',4,4',5-pentachlorobiphenyl (PCB 126), 2,3,7,8-tetrachorodibenzo-*p*-dioxin (TCDD), or an extract derived from field-collected cormorant eggs injected into double-crested cormorant (*Phalacrocorax auritus*) eggs, *Environ. Toxicol. Chem.*, 16, 1450, 1997a.
382. Nosek, J. A., Sullivan, J. R., Hurley, S. S., Olson, J. R., Craven, S. R., and Peterson, R. E., Metabolism and disposition of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in ring-necked pheasant hens, chicks, and eggs, *Toxicol. Environ. Health*, 35, 1992, 153.

383. Nosek, J. A., Sulivan, J. R., Amundson, T. E., Craven, S. R., Miller, L. M., Fitzpatrick, G., Cook, M. E., and Peterson, R. E., Embryotoxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in ring-necked pheasants, *Arch. Environ. Contam. Toxicol.*, 23, 1993, 250.
384. Hudson, R., Tucker, R., and Haegele, M., *Handbook of Toxicity of Pesticides to Wildlife*, 2nd ed., U.S. Fish and Wildlife Service, Resources Publication No. 153, Washington, D.C.
385. Harris, H. J., Erdman, T. C., Ankley, G. T., and Lodge, K. B., Measures of reproductive success and PCB residues in eggs and chicks of Forster's tern on Green Bay, Lake Michigan — 1988, *Arch. Environ. Contam. Toxicol.*, 25, 304, 1993.
386. Kubiak, T. J., Harris, H. J., Smith, L. M., Schwartz, T. R., Stalling, D. L., Trick, J. A., Sileo, L., Docherty, D. E., and Erdman, T. C., Microcontaminants and reproductive impairment of the Forster's tern on Green Bay, Lake Michigan — 1983, *Arch. Environ. Contam. Toxicol.*, 18, 706, 1989.
387. Hoffman, D. J., Rattner, B. A., Sileo, L., Docherty, D., and Kubiak, T. J., Embryotoxicity, teratogenicity and aryl hydrocarbon hydroxylase activity in Forster's terns on Green Bay, Lake Michigan, *Environ. Res.*, 42, 176, 1987.
388. Smith, L. M., Schwartz, T. R., Feltz, K., and Kubiak, T. J., Determination and occurrence of AHH-active polychlorinated biphenyls, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and 2,3,7,8-tetrachlorodibenzofuran in Lake Michigan sediment, and biota. The question of their relative significance, *Chemosphere*, 21, 1063, 1990.
389. Schwartz, T. R. and Stalling, D. L., Chemometric comparison of polychlorinated biphenyl residues and toxicologically active polychlorinated biphenyl congeners in the eggs of forster's terns (*Sterna fosteri*), *Arch. Environ. Contam. Toxicol.*, 20, 183, 1991.
390. Schwartz, T. R., Tillitt, D. E., Feltz, K. P., and Peterman, P. H., Determination of mono- and non-o,o'-chlorine substituted polychlorinated biphenyls in aroclors and environmental samples, *Chemosphere*, 26, 1443, 1993.
391. King, K. A., Custer, T. W., and Quinn, J. S., Effects of mercury, selenium, and organochlorine contaminants on reproduction of Forster's terns and black skimmers nesting in a contaminated Texas bay, *Arch. Environ. Contam. Toxicol.*, 20, 32, 1991.
392. Ludwig, J. P., Auman, H. J., Kurita, H., Ludwig, M. E., Campbell, L. M., Giesy, J. P., Tillitt, D. E., Jones, P., Yamashita, N., Tanabe, S., and Tatsukawa, R., Caspian tern reproduction in the Saginaw Bay ecosystem following a 100-year flood event, *J. Great Lakes Res.*, 19, 96, 1993.
393. Grasman, K. A., Fox, G. A., Scanlon, P., and Ludwig, J. P., Organochlorine-associated immunosuppression in prefledgling Caspian terns and herring gulls from the Great Lakes: An ecoepidemiological study, *Environ. Health Perspect.*, 104, 829, 1996.
394. Brunstrom, B., Toxicity of coplanar polychlorinated biphenyls in avian embryos, *Chemosphere*, 19, 765, 1989.
395. Brunstrom, R., Andersson, L., Nikolaidis, E., and Dencker L., Non-ortho- and mono-ortho-chlorine-substituted polychlorinated biphenyls-embryotoxicity and inhibition of lymphocyte development, *Chemosphere*, 20, 1125, 1990.
396. Elliott, J. E., Kennedy, S. W., Peakall, D. B., and Won, H., Polychlorinated biphenyl (PCB) effects on hepatic mixed function oxidases and porphyria in birds. I. Japanese quail, *Comp. Biochem. Physiol.*, 96C, 205, 1990.
397. Elliott, S. E., Kennedy, S. W., Jeffrey, D., and Shutt, L., Polychlorinated biphenyl (PCB) effects on hepatic mixed function oxidases and porphyria in birds. II. American Kestrel, *Comp. Biochem. Physiol.*, 99C, 141, 1991.
398. McKinney, J. D., Chae, K., Gupta, B. N., Moore, J. A., and Goldstein, J. A., Toxicological assessment of hexachlorobiphenyl isomers and 2,3,7,8-tetrachlorodibenzofuran in chicks, *Toxicol. Appl. Pharmacol.*, 36, 65, 1976.
399. Fox, L. L. and Grasman, K. A., Effects of PCB 126 on primary immune organ development in chicken embryos, *J. Toxicol. Environ. Health, Part A*, 58, 233, 1999.
400. Grasman, K. A. and Whitacre, L. L., Effects of PCB 126 on thymocyte surface marker Expression and immune organ development in chicken embryos, *J. Toxicol. Environ. Health, Part A*, 62, 191, 2001.
401. Grasman, K. A. and Fox, G. A., Associations between altered immune function and organochlorine contamination in young Caspian terns (*Sterna caspia*) from Lake Huron, 1997–1999, *Ecotoxicology*, 10, 101, 2001.

402. Grasman, K. A., Armstrong, M., Hammersley, D. L., Scanlon, P., and Fox, G. A., Geographic variation in blood plasma protein concentrations of young herring gull (*Larus argentatus*) and Caspian terns (*Sterna caspia*) from the Great Lakes and Lake Winnipeg, *Compar. Biochem. Physiol., Part C*, 125, 365, 2000.
403. Mora, M. A., Auman, H. J., Ludwig, J. P., Giesy, J. P., Verbrugge, D. A., and Ludwig, M. E., Polychlorinated biphenyls and chlorinated insecticides in plasma of caspian terns: Relationships with age, productivity, and colony site tenacity in the Great Lakes, *Arch. Environ. Contam. Toxicol.*, 24, 320, 1993.
404. Powell, D. C., Aulerich, R. J., Meadows, J. C., Tillitt, D. E., Stromborg, K. L., Kubiak, T. J., Giesy, J. P., and Bursian, S. J., Organochlorine Contaminants in double-crested cormorants from Green Bay, Wisconsin. II. Effects of an extract derived from cormorant eggs on the chicken embryo, *Arch. Environ. Contam. Toxicol.*, 32, 316, 1997b
405. Gilman, A. P., Hallett, D. J., Fox, G. A., Allan, L. J., and Peakall, D. B., Effects of injected organochlorines on naturally incubated herring gull eggs, *J. Wildl. Manage.*, 42, 484, 1978
406. Fox, G. A., Collins, B., Hayaskawa, E., Weseloh, D. V., Ludwig, J. P., Kubiak, T. J., and Erdman, T. C., Reproductive outcomes in colonial fish-eating birds: A biomarker for developmental toxicants in Great Lakes food chains. II. Spatial variation in the occurrence and prevalence of bill defects in young double-crested cormorants in the Great Lakes, *J. Great Lakes Res.* 17, 158, 1991.
407. Yamashita, N., Tanabe, S., Ludwig, J. P., Kurita, H., Ludwig, M. E., and Tatsukawa, R., Embryonic abnormalities and organochlorine contamination in double-crested cormorants (*Phalacrocorax auritus*) and Caspian terns (*Hydroprogne caspia*) from the upper Great Lakes, *Environ. Pollut.*, 79, 163, 1993.
408. Klasing, K. C., Vitamins, in *Comparative Avian Nutrition*, CAB International, New York, 1998, Chap. 11.
409. Elaroussi, M. A., DeLuca, H., Forte, L. R., and Biellier, H. V., Survival of vitamin D-deficient embryos: Time and choice of chlolecalciferol or its metabolites for treatment in ovo, *Poult. Sci.*, 72, 1118, 1993.
410. Joyner, C. J., Peddie, M. J., and Taylor, T. G., The effect of vitamin D deficiency on yolk formation in the hen, *Biochem. Soc. Trans.*, 14, 341, 1986.
411. Tillitt, D. E., Ankley, G. T., Giesy, J. P., Ludwig, J. P., Kurita-Matsuba, H., Weseloh, D. V., Ross, P. S., Bishop, C. A., Sileo, L., Stromborg, K. L., Larson, J., and Kubiak, T. J., Polychlorinated biphenyl residues and egg mortality in double-crested cormorants from the Great Lakes, *Environ. Toxicol. Chem.*, 11, 1281, 1992.
412. Sanderson, J. T., Kennedy, S. W., and Giesy, J. P., *In vitro* induction of ethoxyresorufin-o-deethylase and porphyrins by halogenated aromatic hydrocarbons in avian primary hepatocytes, *Environ. Toxicol. Chem.*, 17, 2006, 1998.
413. Bleavins, M. R., Aulerich, R. J., Ringer, R. K., and Bell, T. G., Excessive nail growth in the European ferret induced by Aroclor 1242, *Arch. Environ. Contam. Toxicol.*, 11, 305, 1982.
414. Jackson, T. and Halbert, L., A toxic syndrome associated with the feeding of polybrominated biphenyl-contaminated protein concentrate to dairy cattle, *J. Am. Vet. Med. Assoc.*, 165, 437, 1974.
415. Allen, J. R., Barsotti, D. A., van Miller, J. P., Abrahamson, L. J., and Lalich, J. J., Morphological changes in monkeys consuming a diet containing low levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *Food Cosmet. Toxicol.*, 15, 401, 1977.
416. Morrisey, R. E. and Schwetz, B. A., Reproductive and developmental toxicity in animals, in *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*, 2nd ed., Kimbrough, R. D. and Jensen, A. A., Eds., Elsevier, Amsterdam, 1989, 195.
417. Hochstein, J. R., Bursian, S. J., and Aulerich, R. J., Effects of dietary exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in adult female mink (*Mustela vison*), *Arch. Environ. Contam. Toxicol.*, 35, 348, 1998.
418. Render, J. A., Hochstein, J. R., Aulerich, R. J., and Bursian, S. J., Proliferation of periodontal squamous epithelium in mink fed 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), *Vet. Hum. Toxicol.*, 42, 85, 2000.
419. Render, J. A., Aulerich, R. J., Bursian, S. J., and Nachreiner, R., Proliferation of maxillary and mandibular periodontal squamous cells in mink fed 3,3',4,4',5-pentachlorobiphenyl (PCB 126), *J. Vet. Diagn. Invest.*, 12, 477, 2000.
420. McNulty, W. P., Toxicity and fetotoxicity of TCDD, TCDF and PCB isomers in rhesus macaques (*Macaca mulatta*), *Environ. Health Perspect.*, 60, 77, 1985.

421. Hotton, D., Davideau, J. L., Dupret, J. M., Pike, J. W., Mathieu, H., and Berdal, A., Effects of 1,25-dihydroxyvitamin D3 in the tooth germ. Modulations of the receptor throughout development, *C.R. Seances Soc. Biol. Ses Fil.*, 185, 482, 1991.
422. Andrews, J. E., Polychlorinated biphenyl (Aroclor 1254) induced changes in femur morphometry, calcium metabolism and nephrotoxicity, *Toxicology*, 57, 83, 1989.
423. Restum, J., Bursian, S., Giesy, J., Render, J., Helferich, W., Shipp, E., Verbrugge, D., and Aulerich, R., Multigenerational study of the effects of consumption of PCB-contaminated carp from Saginaw Bay, Lake Huron, on mink. 1. Effects on mink reproduction, kit growth and survival, and selected biological parameters, *J. Toxicol. Environ. Health*, 54, 343, 1998.
424. Heaton, S. N., Bursian, S. J., Giesy, J. P., Tillitt, D. E., Render, J. A., Jones, P. D., Verbrugge, D. A., Kubiak, T. J., and Aulerich, R. J., Dietary exposure on mink to carp from Saginaw Bay, Michigan. 2. Hematology and liver pathology, *Arch. Environ. Contam. Toxicol.*, 29, 411, 1995.
425. Giesy, J. P., Verbrugge, D. A., Othout, R. A., Bowerman, W. W., Mora, M. A., Jones, P. D., Newstead, J. L., Vandervoort, C., Heaton, S. N., Aulerich, R. J., Busian, S. J., Ludwig, J. P., Dawson, G. A., Kubiak, T. J., Best, D. A., and Tillitt, D. E., Contaminants in fishes from Great Lakes-influenced sections and above dams of three Michigan rivers. II. Implications for health of mink, *Arch. Environ. Contam. Toxicol.*, 27, 213, 1994.
426. Paasivirta, J., *Chemical Ecotoxicology*, Lewis Publishers, Chelsea, MI, 1991, 127.
427. Reijnders, P. J. H., Reproductive failure in common seals feeding on fish from polluted coastal waters, *Nature*, 324, 456, 1986.
428. Clark, D. R., Jr. and Lamont, T. G., Organochlorine residues and reproduction in the big brown bat, *J. Wildl. Manag.*, 40, 249, 1974.
429. Clark, D. R. and Krynitsky, A. K., Organochlorine residues and reproduction in the little brown bat, Laurel, Maryland-June 1976, *Pest. Monit. J.*, 12, 113, 1978.
430. Reinhold, J. O., Hendriks, A. J., Slager, L. K., and Ohm, M., Transfer of microcontaminants from sediment to chironomids, and the risk for the Pond bat *Myotis dasycneme* (Chiroptera) preying on them, *Aquat. Ecol.*, 33, 363, 1999.
431. Mason C. and Wren, C. D., Carnivora, in *Ecotoxicology of Wild Mammals*, Shore R. and Rattner, B. A., Eds., Wiley, London, 2001, Chap. 7.
432. Ross, P. S. and Troisi, G. M., Pinnipedia, in *Ecotoxicology of Wild Mammals*, Shore, R. and Rattner, B. A., Eds., Wiley, London, 2001, Chap. 8.
433. O'Shea, T. J. and Aguilar, A., Cetacea and Sirenia. in *Ecotoxicology of Wild Mammals*, Shore, R. and Rattner, B.A., Eds., Wiley, London, 2001, Chap. 9.
434. Kannan, K., Blankenship, A. L., Jones, P. D., and Giesy, J. P., Toxicity reference values for the toxic effects of polychlorinated biphenyls to aquatic mammals, *Hum. Ecol. Risk Assess.*, 6, 181, 2000.
435. Brouwer, A., Reijnders, P. J. H., and Koeman, J. H., Polychlorinated biphenyl (PCB)-contaminated fish induces vitamin A and thyroid hormone deficiency in the common seal (*Phoca vitulina*), *Aquat. Toxicol. (Amsterdam)*, 15, 99, 1989.
436. *Ambio* Special Issue: Seals and Seal Protection, 21, 1992.
437. Swart, R. L. De., Ross, P. S., Timmerman, H. H., Vos, H. W., Reijnders, P. J. H., Vos, J. G., and Osterhaus, A. D. M. E., Impaired cellular immune response in harbor seals (*Phoca vitulina*) feeding on environmentally contaminated herring, *Clin. Exp. Immunol.*, 101, 480, 1995.
438. Troisi, G. M. and Mason, C., Cytochromes P450, P420 and mixed-function oxidases as biomarkers of polychlorinated biphenyl (PCB) exposure in harbor seals (*Phoca vitulina*), *Chemosphere*, 35, 1933, 1997.
439. Young, D., Becerra, M., Kopec, D., and Echols, S., GC/MS analysis of PCB congeners in blood of the harbor seal Phoca vitulina from San Francisco Bay, *Chemosphere*, 37, 4, 1998.
440. Shaw, S. D., Brenner, D., Hong, C. S., Bush, B., and Shopp, G. M., Low-level exposure to PCBs is associated with immune and endocrine disruption in neonatal harbor seals (Phoca vitulina) from the California coast, *Organohalogen Compd.*, 42, 11, 1999.
441. Bergman, A. A., Health condition of the Baltic grey seal (*Halichoerus grypus*) during two decades, Gynaecological health improvement but increased prevalence of chronic ulcers, *APMIS*, 107, 270, 1999.
442. Harding, L. E., Harris, M. L., Stephen, C. R., and Elliott, J. E., Reproductive and morphological condition of wild mink (*Mustela vison*) and river otters (*Lutra canadensis*) in relation to chlorinated hydrocarbon contamination, *Environ. Health Perspect.*, 107, 141, 1999.

443. Gray, L. E., Jr., Wolf, C., Lambright, C., Mann, P., Price, M., Cooper, R. L., and Ostby, J., Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, *p,p'*-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat, *Toxicol. Ind. Health*, 15, 94, 1999.
444. Muir, D. A., Braune, B., DeMarch, B., Norstrom, R., Wagemann, R., Lockhart, L., Hargrave, L., Bright, D., Addison, R., Payne, J., and Reimer, K., Spatial and temporal trends and effects of contaminants in the Canadian Arctic marine ecosystem: A review, *Sci. Total Environ.*, 230, 83, 1999.
445. Oehme, M., Biseth, A., Schlabach, M., and Wiig, O., Concentrations of polychlorinated dibenzo-*p*-dioxins, dibenzofurans and non-*ortho* substituted biphenyls in polar bear milk from Svalbard Norway, *Environ. Pollut.*, 90, 401, 1995.
446. Wiig, O., Derocher, A. E., Cronin, M. M., and Skaare, J. U., Female pseudohermaphrodite polar bears at Svalbard, *J. Wildl. Dis.*, 34, 792, 1998.
447. Skaare, J. U., Bernhoft, A., Derocher, A., Gabrielsen, G. W., Goksoyr, A., Henriksen, E., Larsen, H. J., Lie, E., and Wiig, O., Organochlorines in top predators at Svalbard: Occurrence, levels and effects, *Toxicol. Lett.*, 112–113, 103, 2000.
448. De Guise, S., Martineau, D., Beland, P., and Fournier, M., Possible mechanisms of action of environmental contaminants on St. Lawrence beluga whales (*Delphinapterus leucas*), *Environ. Health Perspect.*, 103, 73, 1995.
449. Lahvis, G. P., Wells, R. S., Kuehl, D. W., Stewart, J. L., Rhinehart, H. L., and Via, C. S., Decreased lymphocyte responses in free-ranging bottlenose dolphins (*Tursiops truncatus*) are associated with increased concentrations of PCBs and DDT in peripheral blood, *Environ. Health Perspect.*, 103, 67, 1995.
450. Barber, T. R., Chappie, D. J., Duda, D. J., Fuchsman P. J., and Finley, B. L., Using a spiked sediment bioassay to establish a no-effect concentration for dioxin exposure to the amphipod Ampelisca abdita, *Environ. Toxicol. Chem.*, 17, 420, 1998.
451. Ashley, C. M., Simpson, M. G., Holdich, D. M., and Bell, D. R., 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin is a potent toxin and induces cytochrome P450 in the crayfish, *Pacifastacus leniusculus*, *Aquat. Toxicol. (Amsterdam)*, 35, 157, 1996.
452. Hahn, M., Karchner, S., Shapiro, M., and Perera, S., Molecular evolution of two vertebrate aryl hydrocarbon (dioxin) receptors (AHR1 and AHR2) and the PAS family, *Proc. Natl. Acad. Sci. U.S.A.*, 94, 13743, 1997.
453. Powell, C. J., Bradfield, C., and Wood, W., *Caenorhabditis elegans* orthologs of the aryl hydrocarbon receptor and its heterodimerization partner the aryl hydrocarbon receptor nuclear translocator, *Proc. Natl. Acad. Sci.U.S.A.*, 95, 2844, 1998.
454. Adams, J. A. and Haileselassie, H. M., The effects of polychlorinated biphenyls (Aroclors 1016 and 1254) on mortality, reproduction, and regeneration in *Hydra oligactis*, *Arch. Environ. Contam. Toxicol.*, 13, 4913, 1984.
455. EPA, Ambient water quality criteria for polychlorinated biphenyls, U.S. Environmental Protection Agency Rep., 440/5–80–068, 1980, 221.
456. MacDonald, D. D., Ingersoll, C. G., and Berger, T. A., Development and evaluation of consensus-based sediment quality guidelines, *Arch. Environ. Contam. Toxicol.*, 39, 20, 2000.
457. Huang, Y-W., Melancon, M. J., Jung, R. E., and Karasov, W. H., Induction of cytochrome P450-associated monooxygenases in northern leopard frogs, *Rana pipiens*, by 3,3',4,4',5-pentachlorobiphenyl, *Environ. Toxicol. Chem.*, 17, 1564, 1998.
458. Huang, Y-W., Karasov, W. H., Patnode, K. A., and Jefcoate, C. R., Exposure of northern leopard frogs in the Green Bay ecosystem to polychlorinated biphenyls, polychlorinated dibenzo-*p*-dioxins, and polychlorinated dibenzofurans is measured by direct chemistry but not by hepatic ethoxyresorufin-*o*-deethylase activity, *Environ. Toxicol. Chem.*, 18, 2123, 1999.
459. Huang, Y-W., and Karasov, W. H., Oral bioavailability and toxicokinetics of 3,3',4,4',5-pentachlorobiphenyl in northern leopard frogs, *Rana pipiens*, *Environ. Toxicol. Chem.*, 19, 1788, 2000.
460. Sparling, D. W., Ecotoxicology of organic contaminants to amphibians, in *Ecotoxicology of Amphibians and Reptiles*, Sparling, D. W., Linder, G., and Bishop, C. A., Eds., SETAC Press, Pensacola, FL, 2000, Chap. 8a.

461. Portelli, M. J. and Bishop, C. A., Ecotoxicology of organic contaminants in reptiles: A review of the concentrations and effects of organic contaminants in reptiles, in *Ecotoxicology of Amphibians and Reptiles,* Sparling, D. W., Linder, G., and Bishop, C. A., Eds., SETAC Press, Pensacola, FL, 2000, Chap. 8b.