CHAPTER 2.2

EXPOSURE AND EFFECTS

OF

AIRBORNE CONTAMINATION

for the

Great Waters Program Report

United States Environmental Protection Agency

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Abstract: The chemical properties and the extensive historic utilization of a number of residue-forming xenobiotic substances of anthropogenic origin have led to the ubiquitous distribution of these materials throughout the global environment. The contention is supported by a substantial body of literature which has documented the presence of anthropogenic contaminants in areas presumably remote from the direct industrial and/or cultural influences attributable to humans. The purpose of the chapter is to examine the existing scientific literature related to atmospherically transported contaminants and summarize present knowledge about the types and kinds of chemical contaminants of concern, the pathways and processes involved in exposure, and the multiplicity of effects associated with these substances. Then, having examined the present base of information, efforts will be made to identify knowledge gaps and information deficits. From this basis, future information needs can be identified.

DISCLAIMER

This document was prepared by researchers in Great Waters-related scientific disciplines, and a draft of this report was reviewed by an expanded group of scientists at a workshop held in November 1992 in Chapel Hill, North Carolina. Other workshop participants included representatives from the U.S. Environmental Protection Agency, the National Oceanic and Atmospheric Administration, the International Joint Commission, and the affected States.

This report has been reviewed by the Office of Air Quality Planning and Standards, Pollutant Assessment Branch, U.S. Environmental Protection Agency, and has been approved for distribution as received from the team of authors. Approval does not signify that the contents reflect the views and policies of the U.S. Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

2.2 EXPOSURE AND EFFECTS OF AIRBORNE CONTAMINANTS: PUBLIC HEALTH AND ENVIRONMENTAL IMPACTS

2.2.1 Introduction

The chemical properties and the extensive historic utilization of a number of residue-forming xenobiotic substances of anthropogenic origin have led to the ubiquitous distribution of these materials throughout the global environment. This contention is supported by a substantial body of literature which has documented the presence of anthropogenic contaminants in areas presumably remote from the direct industrial and/or cultural influences attributable to humans. These remote sites have included snow in the Antarctic (Peterle 1969; Peel 1975), mammals of the Arctic (Bowes and Jonkel 1975; Clausen et al. 1973), in the surface waters and atmosphere above the Sargasso Sea (Bidleman and Olney 1974), rainfall in the South Pacific Ocean (Benvenue et al. 1972), remote island sites in the North American Great Lakes (Murphy and Rzeozutko 1977; Swain 1978; Swackhamer et al. 1988; Swackhamer and Hites 1988), and in the surface waters of most of the world's oceans, including the Atlantic Gulf stream, the Sargasso Sea, the continental shelves of Iceland, Ireland, Norway, Portugal (Ballschmiter et al. 1981), the Caspian Sea, the North Pacific and Antarctic Oceans (Zell and Ballschmiter 1980a), the North Sea and North Atlantic Ocean (Ballschmiter et al. 1978; Zell and Ballschmiter 1980b). Given this world-wide distribution, it is not surprising, then, that one of the chief mechanisms involved in the movement of these compounds is atmospheric transport.

Large aquatic and marine ecosystems are morphometrically — and hence, physically, chemically, and biologically — predisposed to excessive susceptibility to toxic chemical insult. Many large aquatic, estuarian, or coastal marine ecosystems are geographically located in physical proximity to large population centers, and hence, pollution sources. Atmospherically-derived contamination to these systems is quantitatively significant because of the vast surface areas of these water bodies. Atmospheric inputs are particularly significant to large aquatic and marine ecosystems, since the contribution is direct, and not filtered through soils and sediments, as is often the case for tributary derived pollutants (Sonzogni and Swain 1980).

These large ecosystems are frequently oligotrophic in nature, i.e., they are relatively unproductive with a relatively low autochthonous production of particulate matter. Further, because of their low suspended sediment load per unit volume, the opportunity for sorption, scavenging, and subsequent removal to the sediments is markedly decreased. Low solids burdens and decreased volumetric inputs of particulate matter also diminish the capacity of these systems to dilute the concentrations of toxic materials once they have been deposited in the bottom sediments.

Because of the enormous depth of some of these ecosystems, the length of time required for even the low quantities of particulate matter available to settle to the bottom is excessive, allowing a considerable period for exposure of fish and other biota to the particulate-borne contaminants. The increased time of retention of toxic substances in the water column is also

aided by wind-driven circulation, resuspension and mixing in the water column (Sonzogni and Swain 1980). Hydraulic detention times of the order of decades to centuries have been calculated for some of these large ecosystems (Quinn 1992). All of these factors tend to increase the opportunity for exposure of the biota to toxic chemical insult, primarily because natural removal mechanisms function at such a slow rate.

Finally because of their trophic status, these systems are likely to contain highly sensitive biota in which one or more life stages may be particularly sensitive to the influence of toxic contaminants. The question of human exposure potential is also involved, because the biota of the upper trophic levels are regarded as highly desirable by commercial fish harvesters and sports and subsistence anglers.

The purpose of this chapter is to examine the existing scientific literature related to atmospherically transported contaminants and summarize present knowledge about the types and kinds of chemical contaminants of concern, the pathways and processes involved in exposure, and the multiplicity of effects associated with these substances. Then, having examined the present base of information, efforts will be made to identify knowledge gaps and information deficits. From this basis, future information needs can be identified which will serve to indicate new or expanded research directions required for the coming decade.

2.2.2 Elements of Atmospheric Transport

The ubiquitous global distribution of many of the contaminants of concern, particularly the residue-forming organochlorine compounds, has been well documented. A number of the compounds commonly included in this group of contaminants of concern have had their North American production and usage severely curtailed or eliminated in the 1970 to 1983 time period. Despite this fact, these compounds continue to be reported in biologic tissues taken from large aquatic and marine systems, both in North America and throughout the world (Veith et al. 1977; Norstrom et al. 1980; Schmitt et al. 1981; Schmitt et al. 1985; Ahlborg et al. 1992). The environmental persistence of these compounds (Ballschmiter et al. 1978) is only a partial explanation for these continued observations. It is reasonable to expect observations of these compounds whose biological half-lives are of the order of years to decades to persist in biological tissue, particularly in long-lived species. However, it is less reasonable to anticipate that these compounds might be so uniformly observed in fresh mobile sediments and in the water column itself (Glooschenko et al. 1976; Frank et al. 1977; Swain 1978; Eisenreich and Johnson 1983). Atmospheric transport of residue-forming xenobiotic compounds provides an explanation for the continued observation of these compounds in a variety of environmental media (Strachan and Huneault 1979; Eisenreich et al. 1981). The short- and intermediate-range aerial transport of these substances is well recognized (Olie et al. 1977; Olie et al. 1983; Hutzinger et al. 1985; Kuehl et al. 1985). Long-range atmospheric movement of the order of hundreds to thousands of kilometers has frequently been implicated by existing data (Risebrough et al. 1968; Seba and Prospero 1971, 1972; Spencer 1974; Peakall 1976; Hoff et al. 1992a, b), but only in a few instances has it been possible to directly associate the observation of the compounds of concern

in atmospheric or precipitation samples with an environmental application or incident (Cohen and Pinkerton 1966; Rice and Evans 1984; Swain et al. 1986).

Except immediately downwind from a substantial source of contamination, the atmosphere does not represent a significant reservoir for most organic compounds. To illustrate this facet, the contemporary burdens of polychlorinated biphenyls (PCBs) for a variety of environmental media in the Great Lakes basin are presented in Table 1.

While the atmosphere is not typically a substantial reservoir for contaminants, atmospheric transport is frequently the major pathway by which contaminants enter marine and large aquatic ecosystems. The data from the International Joint Commission (1987) suggest the magnitude of the atmospheric loading of PCBs to the Great Lakes (Figure 1). More than half of the total PCB loading to the Upper Great Lakes (Lake Superior, 90 percent, Lake Huron, 78 percent, Lake Michigan, 58 percent) is the result of the direct or indirect contribution of the atmosphere.

Once a compound of concern has entered the atmosphere, either in the form of a particulate or vapor phase emission, it is possible for these materials to travel great distances. The transport of contaminants is dependent upon a number of factors including air currents, particle size, vapor pressure, vapor partitioning, scavenging of particles by water droplets, washout phenomena, and particle settling (Strachan and Huneault 1979; Eisenreich et al. 1981; Eisenreich and Johnson 1983; Murphy 1984). While a complete discussion of these factors is beyond the scope of this review, a number of the major processes are summarized below.

2.2.2.1 Physical Properties and Atmospheric Distribution

The organic compounds of concern have varying physical properties, both by individual substance and by compound class. However, despite their individual variation, their general similarities to each other are greater than their differences (Murphy 1984). These organic compounds tend to form persistent residues in various environmental compartments, including biota; they tend to have low vapor pressures ($< 10^{-5}$ atm); and they generally have high solubilities in non-polar liquids and low solubilities in water (< 1 mg/l).

In the atmosphere, trace organic compounds are distributed between the vapor phase and the particulate, or aerosol, phase. Vapor-aerosol partitioning in the atmosphere is a function of the individual compound's vapor pressure, the size, type, and surface area of suspended atmospheric particulates, and the organic content of the aerosol phase. Volatile organic materials, existing as vapor in the atmosphere, can be either adsorbed on the surface of particles, or absorbed by non-polar particulates. The quantity of organic compound adsorbed is a function of the surface area and chemical constituents of the particles in the atmospheric aerosol. The quantity of organic compound absorbed by non-polar particulate matter is determined by the quantity of the particulate matter present and the capacity of those particles for absorption, i.e., their fugacity (Murphy 1984).

TABLE 1

CONTEMPORARY PCB CONCENTRATIONS IN ENVIRONMENTAL MEDIA IN THE GREAT LAKES BASIN

	Air (ng/m^3)[a]	Rain (ng/L)[a]	Water (ng/L)	Sediments (ng/g)
LAKE SUPERIOR				
Mean	0.2	1.0	0.2[b]	9[b]
Range	0.2–0.4	1.0–5.0	0.1–0.3	4–12[b]
LAKE MICHIGAN				
Mean	0.3	2.0	0.63[c]	81[d]
Range	0.1–1.5	---	0.3–1.7[c]	1–201[d]
LAKE HURON				
Mean	0.2	2.0	0.49[e]	---
Range	0.15–0.25	---	0.28–0.57[e]	---
LAKE ERIE				
Mean	0.4	2.0	---	---
Range	0.4–0.5	---	---	---
LAKE ONTARIO				
Mean	0.4	3.0	---	---
Range	0.3–0.5	---	---	---

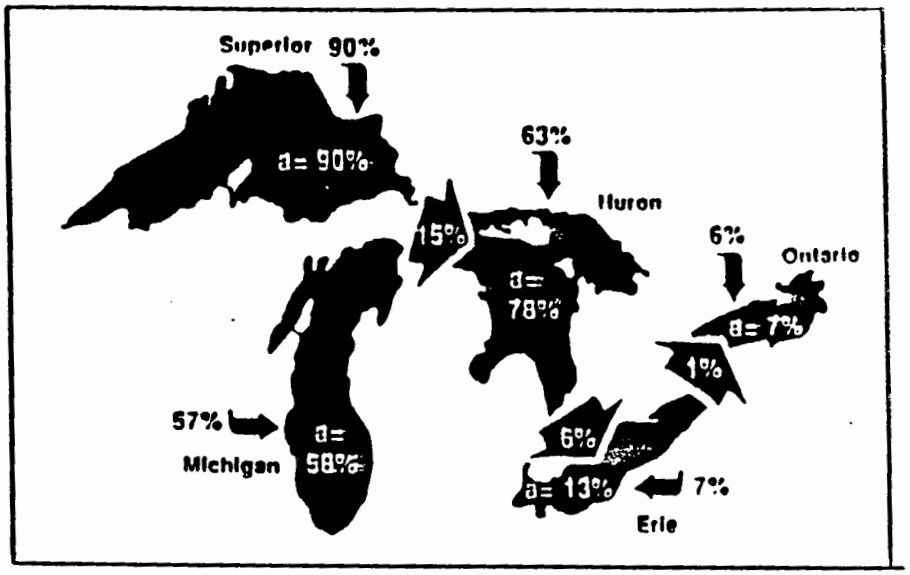
Sources:
a. Eisenreich and Strachan (1992)
b. Eisenreich and Jeremiason (1992)
c. Swackhamer et al. (1992)
d. Swackhamer and Armstrong (1988)
e. Swain et al. (1986)

FIGURE 1

ATMOSPHERIC LOADING OF PCBs TO THE GREAT LAKES

TOTAL INPUTS, kg/yr
(all sources)

Superior	**606**
Michigan	**685**
Huron	**636**
Erie	**2,520**
Ontario	**2,540**



Small arrows indicate atmospheric contribution falling directly on each lake. Large arrows denote indirect atmospheric contribution passed down from lakes "upstream." a = total atmospheric contribution, both direct and indirect.

Source: International Joint Commission (1987)

2.2.2.2 Atmospheric Deposition Processes

There are three dominant processes that transfer organic contaminants from the atmosphere to marine and large aquatic ecosystems. These are: (1) vapor partitioning across the air–water interface; (2) dry deposition; and (3) precipitation (wet) deposition. A brief discussion of the importance of each of these processes is presented below.

Contaminants in the vapor–phase tend to partition directly across the air–water interface. The tendency to move from one medium to another is based upon the fugacity of the individual compound (Mackay 1979; Mackay and Patterson 1981). The fugacity of a compound is a measurement of its tendency to escape from a particular medium into another physical phase or medium. In short, the fugacity of a material is its tendency to partition from one medium to another. If a vapor–phase, airborne contaminant immediately above the surface of the water is at equilibrium with both phases, the air and the water, the fugacity of that contaminant is the same, and no vapor–phase partitioning will occur (Murphy 1984). However, if the fugacity of one phase exceeds that of the other, the contaminant of concern will tend to partition from the phase with the higher fugacity toward the lower.

An example of vapor–phase transfer has been provided by Eisenreich and Looney (1982). These authors made very careful measurements of PCBs in the water column and in the atmosphere under stable atmospheric conditions over Lake Superior. They found significantly higher concentrations of PCBs in the water layer at the surface than in those layers deeper in the water column. These authors reported that atmospheric vapor inputs of low–volatility PCBs were responsible for maintaining the gradient observed in Lake Superior.

The settling of particles onto a surface in the absence of a precipitation event is referred to as dry deposition. Slinn et al. (1978) and Slinn and Slinn (1980) have considered dry deposition to bodies of water. These authors note that the deposition velocity or rate of deposition of an organic compound is a function of the size particle to which it is sorbed. The smallest of the particles have aerodynamic diameters, known as mass median diameters (mmd), of < 0.3 μm. While more dense than air, these particles are small enough to be moved about by Brownian diffusion. Since these particles are unaffected by a gravitational component, their deposition is independent of the orientation of the surface with which they collide. The next larger size particles are those with aerodynamic diameters in the range of 0.5 to 2–5 μm. These particles are deposited on surfaces by impaction. Particles with mmd values greater than 2–5 μm are too large to be seriously influenced by air molecules and Brownian movement. Because their mass is greater, gravity imparts a net downward movement on these particles known as a deposition velocity. Gravitational sedimentation from the atmosphere is the principal removal mechanism for these particles. Ultragiant particles, those particles with aerodynamic diameters (mmd) greater than 10 μm, also have an increased deposition velocity as a function of their increased mass. The relationships of particle size and deposition velocities are shown in Table 2.

Andren and Strand (1981) have shown that 70 percent of the total organic carbon associated with airborne particulate matter over Lake Michigan is transported by particles < 1.0

μm in size. Because of the greater surface-to-volume ratio and higher organic content of particles in this size range, Doskey and Andren (1981a, b) reported that polychlorinated biphenyls (PCBs) are associated with these submicron sized particulates.

Precipitation in the form of rain and snowfall is another major mechanism for the deposition of organic contaminants to large water bodies. In the atmosphere, aerosol particulates are concentrated and removed by a variety of events related to precipitation. Atmospheric particulates serve as droplet condensation nuclei forming clouds. Cloud droplets formed in this manner may also scavenge additional particulate matter from the air mass. Scott (1981) reports that the coalescence of approximately 10^6 cloud droplets in a liter of air can result in an increase in concentration of trace organic compounds by 10^5 to 10^6 in the resulting precipitation by this mechanism. Further, if an organic compound has a tendency to partition into water, vapor phase compounds in the atmosphere can be substantially higher in precipitation.

TABLE 2

RELATIONSHIP OF PARTICLE SIZE TO DEPOSITION MECHANISM AND DEPOSITION VELOCITY (V_D)

PARTICULATE MASS MEDIAN DIAMETER (μm)	DEPOSITION MECHANISM	APPROXIMATE DEPOSITION VELOCITY (m/s)
< 0.3	Brownian diffusion	Isotrophic (~ 0.005)
0.5 to 2 - 5	Inertial Impaction	< 0.002
> 2 - 5	Gravitational Sedimentation	> 0.005

Sources: Eisenreich et al. (1981) and Murphy (1984)

The results of field studies suggest that the bulk of the trace organic contaminants in precipitation is associated with particulate matter. Hence, the majority of the contaminant transferred to a large water body will be deposited in the early stages of a precipitation event. The first few millimeters of precipitation contain relatively high concentrations of the contaminant as a result of atmospheric washout, while the remainder of the precipitation event, containing much reduced concentrations of the contaminant, serves essentially as dilution for the earlier deposition (Strachan and Huneault 1979; Murphy and Rzeszutko 1977).

The amount of variation in contaminant levels in individual precipitation events has been demonstrated by Murphy (1984) and Swain et al. (1986). The variation in precipitation inputs of PCBs to the Great Lakes has been summarized in Table 3.

Swackhamer and Armstrong (1986) have demonstrated the relative importance of these major removal processes by creating a mass balance for PCBs in Lake Michigan. These authors have demonstrated that, for PCBs, the following mass removal hierarchy exists:

wet washout (particles) > wet washout (vapor) > dry deposition (particles).

2.2.2.3 Atmospheric Deposition

Having reviewed the literature for the preceding decade, Eisenreich et al. (1981) summarized the trace organic contaminant concentrations in the atmosphere and in precipitation in the Great Lakes basin. Their findings are presented in Table 4. From the mean values reported (Table 4) for contaminants in air and precipitation, the equations for wet and dry flux were used to achieve an estimate of annual atmospheric loadings to the Great Lakes for the time period. The Eisenreich et al. (1981) data for total annual atmospheric loadings for a variety of atmospherically-borne pollutants are presented in Table 5.

2.2.2.4 Relationships to Water Quality Criteria

Over the last two decades, the United States Environmental Protection Agency (USEPA) has developed water quality criteria for nearly 200 chemical entities and substances. The specific value for each substance adopted by USEPA was based upon exhaustive examination of the scientific literature and knowledge of that particular chemical entity. From that knowledge, criteria were developed designed to be protective under specific scenarios, e.g., acute or chronic criteria for freshwater ecosystems as contrasted to the acute or chronic values for marine systems. In addition, human health criteria were established based upon a lifetime one in a million risk of cancer. The water quality criteria values for a number of contaminating compounds of concern in the world's great waters are presented in Table 6.

Subsequent to the earlier Eisenreich et al. (1981) study of atmospherically transported contaminants (Table 6) (Eisenreich and Strachan 1992) estimated that transport and deposition

TABLE 3

VARIATION IN PRECIPITATION INPUTS OF PCBs TO THE GREAT LAKES

LOCATION	PCB CONCENTRATION (ng/l)	VOLUME OF PRECIPITATION (cm)	METHOD	REFERENCE
Picton (L. Ontario)	32	16	Event	Strachan and Huneault (1979)
Point Pelee (L. Erie)	9	6	Event	Strachan and Huneault (1979)
Goderich (L. Huron)	11	11	Event	Strachan and Huneault (1979)
Nipigon; Batchawana Bay (L. Superior)	26	10	Event	Strachan and Huneault (1979)
Chicago (L. Michigan)	104	39	Event	Murphy and Rzeszutko (1977)
Chicago (L. Michigan)	75	20	Event	Murphy et al. (1982)
Waukegan (L. Michigan)	46	55	Event	Murphy et al. (1982)
Point Betsie (L. Michigan)	12	63	Event	Murphy et al. (1982)
Whitestone Point (L. Huron)	13	34	Event	Murphy et al. (1982)
Tawas Point (L. Huron)	18	--	Snow Cores	Strachan and Huneault (1979)
Lake Superior	38	--	Snow Cores	Strachan and Huneault (1979)
Lake Ontario	43	--	Snow Cores	Strachan and Huneault (1979)
Saginaw Bay (L. Huron)	25	--	Ice Cores	Murphy and Schinsky (1982)
Duluth (L. Superior)	50	13	Snow Event	Swain (1978)
Isle Royale (L. Superior)	230	25	Snow Event	Swain (1978)

Source: Murphy (1984)

TABLE 4

AIRBORNE TRACE ORGANIC CONCENTRATIONS IN THE GREAT LAKES ECOSYSTEM

	Air		Precipitation	
	Range	Mean	Range	Mean
	(ng/m^3)		(ng/L)	
Total PCB	0.4–3	1.0	10 – 100	30
Total DDT	.01–.05	0.03	1 – 10	5
α–BHC	.25–0.4	0.3	1–35	15
γ–BHC	1–4	2	1–15	5
Dieldrin	.01–0.1	0.05	0.5–30	2
HCB	.01–0.1	0.05	0.5–30	2
p,p'methoxychlor	--	1	1–20	8
α–Endosulfan	--	1	1–10	2
ß–Endosulfan	--	1	1–12	3
Total PAH	10–30	20	50–300	100
Anthracene	0.1–1	0.6	1.3–2.3	2
Phenanthrene	0.1–1	0.6	2.0–2.3	2
Pyrene	0.1–4	1.1	1.3–4.5	2
Benz[a]anthracene	0.1–1	0.5	2.6–3.1	.3
Perylene	0.1–2	.06	--	1
Benzo[a] pyrene	0.1–2	1	0.1–3.1	2
TOC	$2–15 \times 10^3$	9×10^3	$1–5 \times 10^5$	2×10^6
DBP	0.5 – 5	2	4–10	6
DEHP	0.5–5	2	4–10	6

Source: Eisenreich et al. (1981)

TABLE 5

TOTAL DEPOSITION OF AIRBORNE TRACE ORGANIC COMPOUNDS TO THE GREAT LAKES (metric tons per year)

	LAKE				
COMPOUND	**Superior**	**Michigan**	**Huron**	**Erie**	**Ontario**
Total PCB	9.8	6.9	7.2	3.1	2.3
Total DDT	0.58	0.40	0.43	0.19	0.14
α-BHC	3.3	2.3	2.4	1.1	0.77
γ-BHC	15.9	11.2	11.6	5.0	3.7
Dieldrin	0.54	0.38	0.55	0.17	0.13
HCB	1.7	1.2	1.2	0.53	0.39
p,p'methoxychlor	8.3	5.9	6.1	2.6	1.9
α-Endosulfan	7.9	5.6	5.8	2.5	1.8
ß-Endosulfan	8.0	5.6	5.8	2.5	1.9
Total PAH	163	114	118	51	38
Anthracene	4.8	3.4	3.5	1.5	1.1
Phenanthrene	4.8	3.4	3.5	1.5	1.1
Pyrene	8.3	5.9	6.1	2.6	1.9
Benz[a] anthracene	4.1	2.9	3.0	1.5	1.1
Perylene	4.8	3.3	3.4	1.5	1.1
Benzo[a]pyrene	7.9	5.6	5.8	2.5	1.8
DBP	16	11	12	5.0	3.7
DEHP	16	11	12	5.0	3.7
Total Organic Carbons	2×20^5	1.4×10^5	1.5×10^5	$.66 \times 10^5$	$.46 \times 10^5$

Source: Eisenreich et al. (1981)

of a number of toxic substances to the Great Lakes region. Appendix III of their report contains a summary of the recent measurements of contaminant concentrations in rainfall. These data are also presented in Table 6 for comparison with the USEPA Water Quality Criteria for surface waters.

In comparing the concentrations of contaminants in rainfall with the water quality criteria for surface waters, it must be recalled that wet deposition is only a fraction of the total contribution of the atmosphere to the world's great waters. Dry deposition is also responsible for addition of substantial quantities of some contaminants. Calculation of the total flux to waterbodies for each of these compounds is beyond the scope of this paper. However, the averages of measured concentration in precipitation are sufficient to suggest the magnitude of the problem of atmospherically transported contaminants.

The data in Table 6 suggests that in four other instances, the concentrations of contaminants in rainfall exceeded the human health criteria for 10^{-6} cancer risk. The compounds in this group consisted of polychlorinated biphenyls (PCBs), dieldrin, dioxin, and DDT. The mean precipitation values of two additional substances, hexachlorobenzene and chlordane, are the same order of magnitude as the published human health criteria. The value of the alpha isomer of hexachlorocyclohexane (HCH) in rainfall exceeds the recalculated value for human health related to water and organisms, as does dieldrin in precipitation. Four other compounds, DDT, toxaphene, benzo(a)pyrene, and chlordane either approach the recalculated human health criteria values in rainfall, or the average rainfall values are of the same order of magnitude as the human health 10^{-6} cancer risk values recalculated from the IRIS database.

It is clear that the water quality criteria are intended to be applied to the world's great waters and to other bodies of surface water. It is alarming to discover that the precipitation which drives these bodies of water, directly or indirectly, contains average concentrations which exceed or approach criteria one or more water quality criteria values. In fact, of the organic compounds examined, only the gamma isomer of HCH meet all the concentration requirements. Three additional substances also meeting all the criteria limits were metals, i.e., arsenic, cadmium, and lead. If nothing more, this comparison is an indication of the extent of the problem posed by atmospherically transported substances.

2.2.3 Compounds of Concern

2.2.3.1 Identification of Compounds of Concern

There are over 65,000 chemicals registered for current use in the United States, with new ones added continuously. Many of these chemicals are released into the environment by discharges into air, water, land, sewer systems, or subsurface. More than 1000 chemicals have been identified in the waters of the Great Lakes. The Toxic Release Inventory, established as part of the Emergency Planning and Community Right–To–Know Act, requires industry that report on over 300 chemicals and chemical categories. Air emissions of these chemicals account for more than 40 percent of all emissions to all media (EPA 1991). In an attempt to reduce these emissions, the Clean Air Act Amendments of 1991 identify 189 hazardous air pollutants for regulation by the EPA.

TABLE 6

CONCENTRATIONS OF THE COMPOUNDS OF CONCERN IN PRECIPITATION COMPARED WITH THE USEPA WATER QUALITY CRITERIA

(All Values $\mu g/\ell$)

					Human Health 10^{-6} Risk Level for Carcinogens				Estimated Mean and (RANGE) of Concentrations in Rainfall
					Published Criteria		Recalculated Values Using IRIS database		
Compound	Acute Criteria (FRESH)	Chronic Criteria (FRESH)	Acute Criteria (MARINE)	Chronic Criteria (MARINE)	WATER AND ORGANISMS	ORGANISMS ONLY	WATER AND ORGANISMS	ORGANISMS ONLY	
PCBs (Total)	2.0	0.014	10.0	0.03	0.000079	0.000079	—	—	0.003 (0.00027–0.008)
Benzo(A)–Pyrene	—	—	—	—	—	—	0.0028	0.0311	0.002 (0.0006–0.0025)
Dieldrin	2.5	0.0019	0.71	0.0019	0.000071	0.000076	0.00014	0.00014	0.0006 (0.0003–0.001)
Hexachloro–benzene	6.0(p)	3.68(p)	—	—	0.00072	0.00074	—	—	0.0001 (0.00001–0.0004)
Dioxin (2,3,7,8–TCDD)	* <0.01	* <0.00001	—	—	0.000000013	0.000000014	—	—	0.00004[a] (0.0000003–0.0001)
DDT	1.1	0.001	0.13	0.001	0.000024	0.000024	0.00059	0.00059	0.001 (0.00008–0.0027)
Toxaphene	0.73	0.0002	0.21	0.0002	0.00071	0.00073	0.00073	0.00075	0.0006 (<0.0001–0.001)
α HCH (BHC)	—	—	—	—	0.0092	0.031	0.0039	0.013	0.005 (0.001–0.012)

TABLE 6 (Cont.)

					Human Health 10^{-6} Risk Level for Carcinogens				Estimated
					Published Criteria		Recalculated Values Using IRIS database		Mean and (RANGE) of
Compound	Acute Criteria (FRESH)	Chronic Criteria (FRESH)	Acute Criteria (MARINE)	Chronic Criteria (MARINE)	WATER AND ORGANISMS	ORGANISMS ONLY	WATER AND ORGANISMS	ORGANISMS ONLY	Concentrations in Rainfall
γ HCH (BHC)	2.0	0.08	0.16	—	0.0186	0.0625	0.019	0.063	.0034 (0.001–0.01)
Chlordane	2.4	0.0043	0.09	0.004	0.00046	0.00048	0.00058	0.00059	0.0002 (0.00003–0.00045)
Lead	83.0+	3.2+	220	8.5	50.0	—	—	—	.004 (0.0007–0.012)
Cadmium	3.9+	1.1+	43.0	9.3	10.0	—	10.0	170	0.002 (ND–0.007)
Mercury	2.4	0.012	2.1	0.025	0.144	0.146	0.14	0.15	0.025 (0.003–0.213)
Arsenic	—	—	—	—	0.0022	0.0175	0.018	0.14	0.0003 (0.0001–0.0004)
Copper									
Zinc									
N, P									

Sources: USEPA 1991 Water Quality Criteria from Health and Ecological Criteria Division of the Office of Science and Technology (G. Glass, personal communication).

Rainfall Concentrations from Eisenreich and Strachan 1992.

(p) = Proposed criterion
* = Insufficient data to develop criterion, value presented is the L.O.E.L. (lowest observed effect level)
a = Comparative rainfall data are for all tetrachlorodibenzo(p)dioxins
\+ = Hardness dependent criteria (100 μg/ℓ $CaCo_3$ used)

Not all of these chemicals present equal degrees of hazard to the environment, as they have differing chemical behaviors, fates, exposure concentrations, and toxic effects. Thus this formidable list of contaminants can be characterized by level of concern based on the above differences. The characteristics that give rise to greater concern include persistence in the environment, measurable toxicity, and the potential for chemicals to build up in animal tissue such that the concentrations increase within the food web. The same chemical properties that cause persistence often contribute to toxicity, to long range transport, and to lipophilicity which allows them to bioaccumulate. This section focuses on those persistent toxic chemicals that move from air to water and can accumulate in food webs.

Many chemicals in the atmosphere have short lifetimes, due to transformation processes such as photolysis or reactions with radicals, or due to rapid removal processes that deposit the contaminant close to its source. Examples of these would include benzene (former) and lead (latter). Chemicals may have high Henry's Law constants such that they do not readily partition from air to water (for example, toluene). The Great Lakes Water Quality Board of the International Joint Commission (GLWQB, 1987) prioritized the contaminants ("IJC Critical Pollutants") in the Great Lakes according to persistence, lipophilicity, and toxicity. These chemicals are of concern in all the Great Waters of the U.S., and are not specific to the Great Lakes. The chemical properties that control the behaviors of persistence, lipophilicity, and toxicity are vapor pressure, aqueous solubility, and the octanol–water partition coefficient, Kow. Compounds with low Henry's Law constants (approximated by the ratio of vapor pressure to aqueous solubility) readily partition from the gas phase to water, and do not readily revolatilize (Mackay 1982). Compounds with low solubilities are usually associated with particles once they are in water, and thus may not be available to undergo transformation reactions. Compounds with high Kows are lipophilic and readily accumulate in fat or lipid tissue of plants and animals. The pollutants considered to be of greatest concern in Great Waters areas are shown in Table 7, along with their physical properties.

2.2.3.2 Occurrence, Prevalence, and Distribution

The compounds of concern are generally found in the vapor phase or on submicron atmospheric particles such that they can be carried long distances from their point of origin and become well–mixed within a given air mass. Furthermore, many of these chemicals no longer derive from atmospheric point sources, but instead are part of a ubiquitous baseline contamination of the atmosphere. Examples include PCBs, PCDDs/DFs, DDT and the other organochlorine pesticides. Many of these are no longer manufactured in this country, but can be found in remote environments as a result of persistence and long–range atmospheric transport and deposition. One of the major sources of PCDDs/DFs is waste incinerator emissions, which are found throughout the country in rough proportion to population. Thus these chemicals have a fairly constant source which increases near urban areas. There are instances of local or point source "hot–spots" for some chemicals of concern (e.g., metals concentrations near smelters; metals and organic chemical concentrations in or adjacent to urban areas); generally the bodies of water under consideration receive atmospheric loadings representative of the entire region. For

instance, PCB concentrations in air are similar in an east–to–west transect over Lake Superior, which are similar in concentration to measurements over Lake Huron. Concentrations over southern Lake Michigan are only slightly higher, likely due to the proximity and influence of Chicago (see Figure 2) (Eisenreich and Strachan 1992). Thus away from large point sources, concentrations are similar across long distances. Concentrations of PCBs in air over Chesapeake Bay are also similar to those over the Great Lakes (Baker, unpublished data). In Chesapeake Bay, chemicals of concern include PCBs, phthalate esters, PAHs, and heavy metals (copper, zinc, and lead) (Helz and Huggett 1987). Helz and Huggett (1987) and Wright et al. (1992) provide an extensive review of the field and laboratory studies which describe wildlife health disturbances observed in Chesapeake Bay and its tributaries. Atmospheric monitoring of these contaminants by Atmospheric Environment Service of Environment Canada indicates that seasonal variations in concentrations are often greater than geographical differences (Hoff et al. 1992a, b). Elevated concentrations due to urban or highly industrialized areas are highly localized. It must be kept in mind, however, that the atmospheric component of urban area sources to overall loadings of contaminants to water bodies may be substantial despite the confined geographical area, due to prevailing wind directions (e.g., the effect of Chicago on southern Lake Michigan). Quantitative estimates of the urban effects on atmospheric loadings of these contaminants to large water bodies are lacking. First order estimates of atmospheric loadings and the relative importance of atmospheric loads compared to non–atmospheric loads have been made for the Great Lakes (Strachan and Eisenreich 1988; Eisenreich and Strachan 1992).

TABLE 7

POLLUTANTS OF CONCERN IN THE GREAT WATERS

AND THEIR PHYSICAL CHEMICAL PROPERTIES

COMPOUND	VAPOR PRESSURE (atm)	SOLUBILITY (mg/L)	KOW	REFERENCE
PCBs	6×10^{-11} to 1×10^{-5}	1.8×10^{-5} to 4	1.99×10^{4} to 1.38×10^{9}	Mackay et al. 1992
B(a)P	3×10^{-12} to 7.2×10^{-12}	0.004 to 0.0063	1.1×10^{4} to 3.2×10^{6}	Mackay et al. 1992
Dieldrin	4.1×10^{-9} (20 C°)	0.186	1.2×10^{4}	Dynamac Corp. 1989
HCB	1.5×10^{-8} to 3.1×10^{-7}	0.005 to 0.008	1.35×10^{4} to 3.16×10^{5}	Mackay et al. 1992
TCDD	2×10^{-12} to 1.3×10^{-9}	7.2×10^{-6} to 0.002	2.4×10^{5} to 3×10^{8}	Mackay et al. 1992
TCDF	2×10^{-11} to 1.2×10^{-9}	0.0004 to 0.0035	1.35×10^{4} to 3.16×10^{5}	Mackay et al. 1992
DDT	2.5×10^{-10} (20 C°)	0.0031 to 0.0034	1.54×10^{6}	Verschueren 1983
Toxaphene	2.6×10^{-4} to 5.3×10^{-4} (20 C°)	0.3	2×10^{3}	Clement Assoc. 1990
a-HCH	2.89×10^{-4} (20 C°)	0.088	2.88×10^{3} to 7.08×10^{3}	Clement Assoc. 1989
g-HCH	1.24×10^{-8} (20 C°)	17	1.99×10^{3} to 4.07×10^{3}	Clement Assoc. 1989
Chlordane	2.9×10^{-8} to 3.8×10^{-8}	0.056	3.47×10^{5}	Clement Assoc. 1989
nonachlor	n.a.	n.a.	n.a.	
Lead				
Cadmium				
Mercury				
Arsenic				

2.2.3.3 Exposure Routes, Pathways, and Processes

Once chemicals are delivered to water surfaces by atmospheric deposition, they are subject to a number of additional other physical, chemical, and biological processes before impacting a biological receptor. A thorough discussion of these processes in sufficient detail is beyond the scope of this chapter; however, the reader is referred to a recent review of organic contaminant behavior in lakes (Swackhamer and Eisenreich 1991). A brief outline follows. Once in the water column, contaminants will partition thermodynamically between particles (suspended sediment), suspended erosional material, phytoplankton, detritus, etc.), dissolved organic material, and it's truly dissolved form. Hydrophobic organic compounds may be entrained and concentrated at the air–water interface known as the surface organic microlayer, a region tens to hundreds of microns thick consisting of high molecular weight macromolecules having both polar and non–polar functionalities. While contaminant concentrations in the surface organic microlayer may be enriched relative to the water column, the mass of contaminant bound up in the microlayer is small overall.

Most of the organic contaminants and metals of concern have high particle–to–water partition coefficients (Kp). The fate of the chemical, its persistence in water, and it's availability to biota are affected by it's distribution between particles, dissolved organic carbon/colloids, and the dissolved phase. For instance, particle–bound contaminants will deposit to and accumulate in sediments. The exposure to chemicals by organisms thus is largely controlled by the phase of the chemical, and it's bioavailability in that phase. The major exposure routes of aquatic pollutants include exposure directly from the dissolved phase in water and from consuming contaminated food of aquatic origin. Exposure from DOC or colloid–associated contaminants is less important (see below). Exposure from water would include dermal exposure by humans, gill uptake by fish, equilibrium with surrounding water by zooplankton, and sorption to surfaces of aquatic plants. Exposure by food consumption occurs through both the pelagic and benthic food webs. Contaminants associated with sediment are grazed by benthic organisms and bottom–feeding fish; contaminants associated with phytoplankton are grazed by herbivores. These trophic levels can then be consumed by higher trophic levels, all the way up to wildlife and humans. Bioaccumulation is the process by which an organism takes up chemical both from water and from food; bioconcentration describes the uptake of chemical from water only. The ratio of contaminant concentration in organism to that in water is known as the bioaccumulation factor. When the bioaccumulation factor is greater than that predicted by thermodynamic equilibrium between organism and water (the bioconcentration factor), biomagnification is said to occur. Bioaccumulation in a pelagic food web is depicted in Figure 3. Thus the type of exposure route, and the relative importance of each, differs for different receptor organisms.

Phytoplankton accumulate contaminants only from water; fish can accumulate them from transport across the gill membrane and by assimilation of contaminated food (the food concentration is dependent on trophic level); human and wildlife exposure is from water consumption and ingestion of contaminated fish (additional non–aquatic routes of exposure are also possible, such as inhalation or other food sources). Because of biomagnification of lipophilic compounds within the food web, top predator exposures in pelagic food webs are

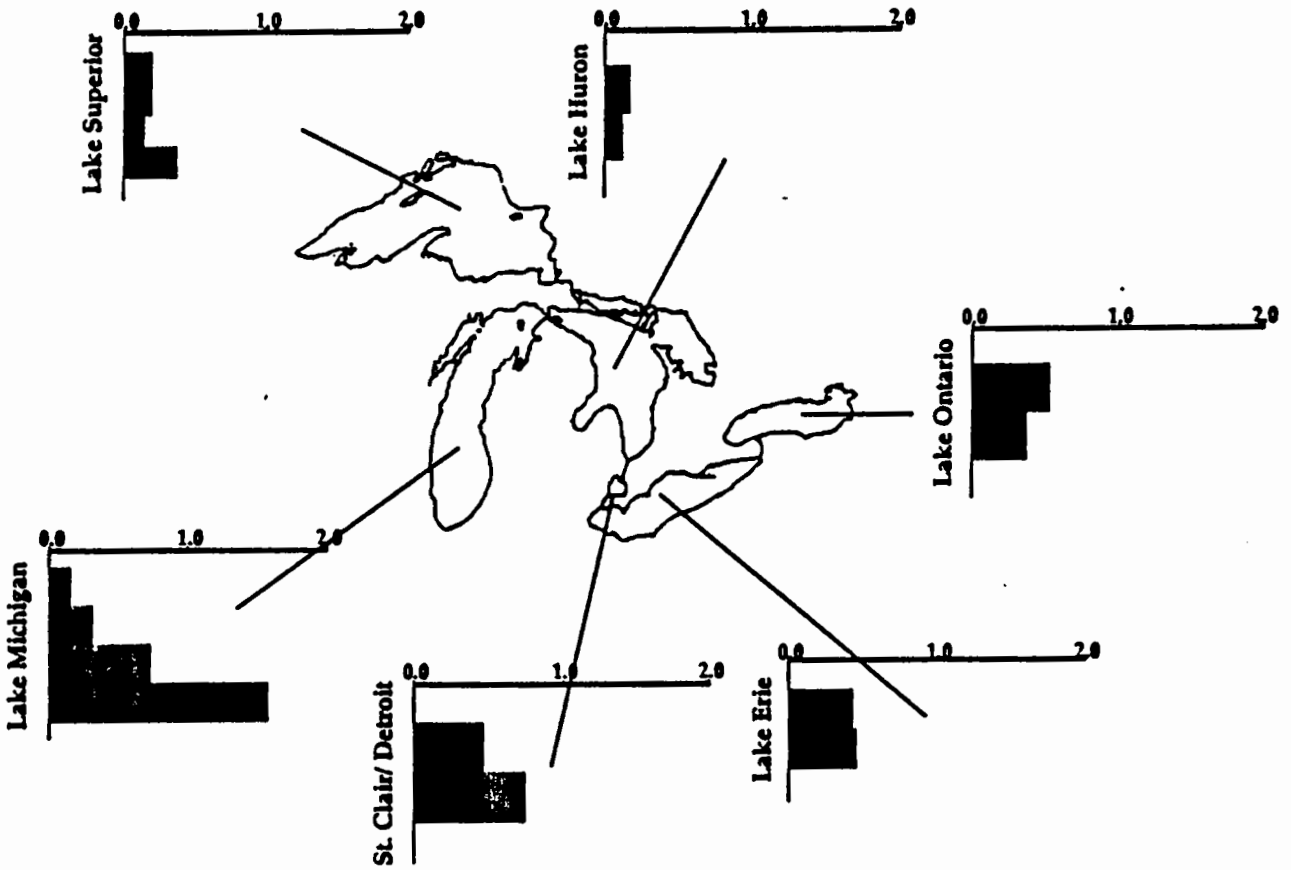
dominated by food consumption rather than from water exposure. For instance, top predators (lake trout) (*Sylvelinus namaycush*) in Lake Michigan are estimated to get 99 percent of their PCB body burden from the food web (Thomann and Connolly 1984). Mackay and coworkers (Mackay et al. 1985) have modeled TCDD exposure to humans, estimating that the major exposure route would be from consuming contaminated fish (Figure 4). Note that contaminants that may be at very low or trace concentrations in water may still be of concern because the biomagnification that can occur within the food web greatly enhances pollutant exposure.

The actual, "effective", concentration of a contaminant is that fraction of contaminant that is actually biologically available. Bioavailability is affected by the water–particle partitioning of the chemical, and by the physical and chemical characteristics of the water body. For toxic metals, the bioavailable form of the metal is affected by pH, temperature, DO, salinity, redox conditions, and complexation reactions. Bioavailability of organic compounds is affected by complexation to DOC (Landrum et al. 1987). There are obvious differences in salinity (and thus possibly exposure and uptake) between marine and freshwater aquatic systems; salinity gradients also exist in estuarine systems such as Chesapeake Bay that vary with time and space, as a function of tides and meteorology. Temperature variations in time, geographical location, and depth of water column occur across all water bodies of concern, and may affect exposure and uptake. Likewise, variations in Ph occur on the micro and macro scales in response to physical, chemical, and biological processes. The effects of these parameters on chemical speciation, complexation, partitioning, and bioavailability are understood to some extent but will not be reviewed here. A full review of the bioavailability literature is beyond the scope of this report, but EPA is encouraged to include such a discussion in future technical support documents.

Temperature, pH, DO and salinity may also alter the internal physiological response of the organism to the contaminant, although little is known on this subject. Potential effects might include alterations in cellular transport, membrane permeability, ionic balance, kinetics of the response, diffusivity of the chemical, and receptor binding. These require much further study.

FIGURE 2

ATMOSPHERIC CONCENTRATIONS OF PCB - FALL AND SPRING 1991-92

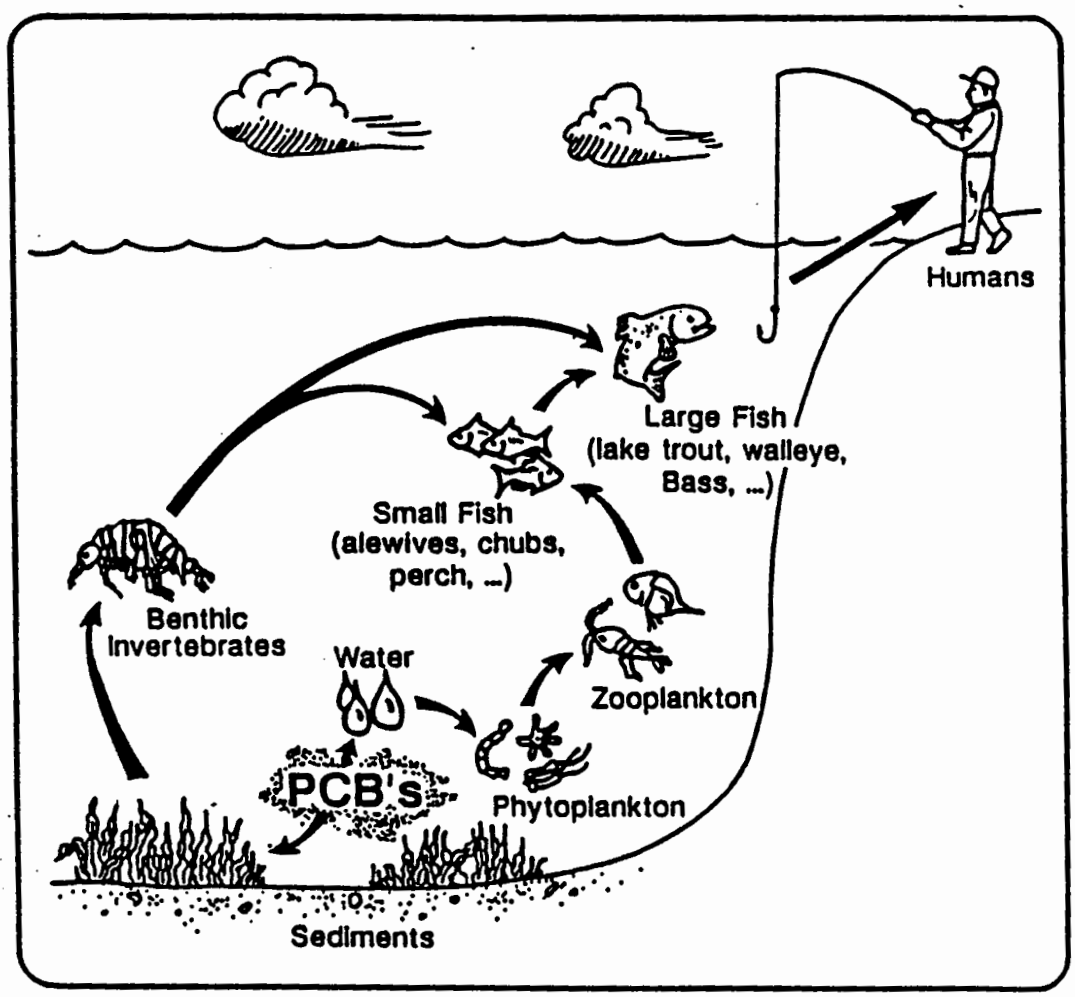


Concentrations of PCBs in air over open waters of the Great Lakes (ng/m3) from fall and spring, 1991-1992. Data are from two to four sites per lake, with each site indicated as a bar on the bar graphs. The spatial distribution of sample locations for each lake, from top to bottom, is as follows: Lake Superior, west to east; Lake Michigan, north to south; Lake Huron, north to south; Lake St. Clair, top is Lake St. Clair, bottom is Detroit River; Lake Erie, east to west; Lake Ontario, east to west.

Source: Hornbuckle, K., and Eisenreich, S.J., Gray Freshwater Biological Institute, University of Minnesota, unpublished data.

FIGURE 3

FOODCHAIN BIOACCUMULATION



Source: Adaptation from WI Sea Grant (1976)

It should be noted that all of the literature reviewed on effects in the field is for northern temperate climates, and may not be fully representative of the effects in aquatic systems in other climates, such as southern California estuaries, the Gulf of Mexico, or the coastal estuaries of Florida. Additional field and experimental work is needed in these areas to document different physical and chemical environments on the effect of contaminants on organisms.

Uptake by animals is affected by the assimilation efficiency of the compound across the gut, the respiration rate (for fish), the metabolic rate, and the egestion rate. The physical form of the contaminant also is important. For instance, the dissolved chemical may be more readily taken up than the same concentration of chemical associated with particles. A quantitative understanding of the effects of these parameters on bioavailability is largely lacking. For instance, the assimilation efficiencies for the vast majority of chemicals for most fish species are unknown.

An accurate characterization of the effective concentration of contaminant is a critical link in demonstrating the connection of atmospheric deposition to water, to organism exposure, to toxic response. Other factors in this linkage will affect the toxic response of an organism. These include the threshold does required to elicit a response (chemical and organism specific), and the kinetics of the response.

The linkage of contaminant deposition to effect has been clearly demonstrated for nitrogen in estuarine systems; it is less clear for the toxic metals and hydrophobic organic compounds. The litany of effects discussed in the next section are potential effects; the demonstration of cause–effect is implicated in the Case Studies in Section 2.2.5, and in the field evidence presented in Section 2.2.4.

The distribution of contaminants between dissolved and particulate phases affects both bioavailability, and the extent to which contaminants are accumulated in food webs relative to other fate pathways. In open waters, much of the particulate phase is composed of phytoplankton. In highly productive waters, hydrophobic contaminants associated with phytoplankton will be removed by sedimentation and buried in the bottom sediments, while less productive waters, a greater percentage of the phytoplankton will be grazed and the associated contaminants transferred preferentially to the food web. Thus, phytoplankton can play a key role in the bioaccumulation process and in affecting exposure of higher organisms to contaminants.

In addition, contaminants can effect phytoplankton primary production and food web structure. Early studies on the effects of PCBs and DDT on marine phytoplankton show that species composition of mixed cultures can be altered as sensitive vs. resistant species and small vs. large species are differently affected. PCB (at 25 ppb) and DDT (at 50 ppb) inhibits growth, in pure cultures, of the marine diatom *Thalassiosira pseudonana*, but not the more resistant green alga *Dunaliella tertiolecta* (Mosser et al. 1972). When placed in mixed cultures, the sensitivity of *T. pseudonana* increased such that its growth was inhibited at PCB concentrations that showed no effect in pure cultures. This result may be due to limited nutrient availability. That is, when uninhibited, *T. pseudonana* assimilates more nutrients than *D. tertiolecta* because of its greater

rate of growth. However, when *T. pseudonana* is impaired by DDT or PCB, more nutrients are available to the resistant *D. tertiolecta* for assimilation. In this way, nutrient availability plays a key role in determining the effects of chemicals on food web structure. A slow growing, less abundant, resistant species may become more prominent at the expense of a sensitive species following chemical exposure. PCBs may impair the growth of *T. pseudonana* by inhibiting membrane-bound enzymes involved in nitrogen metabolism (Fisher 1975).

In 1975, Fisher determined that growth, rather than photosynthetic capability, was reduced in marine algae following PCB (10 ppb) and DDT (50 ppb) exposure. The 72 percent inhibition of *T. pseudonana* culture and the 84 percent inhibition of *S. costatum* culture photosynthesis by DDT were a result of growth inhibition rather than photosynthetic inhibition. Fisher therefore concluded that total marine photosynthesis will not show dramatic decline however, the replacement of sensitive species by dominant species will result in a qualitative rather than quantitative alteration of herbivores' food supply and, subsequently, the marine food web (Fisher 1975). This alteration could prove dramatic if the sensitive species are a primary food source for herbivores.

Moore and Harris (1972) also describe a parallel decline in photosynthesis and growth of natural marine phytoplankton communities following exposure to p,p'-DDT (5 ppb) and 2,4-D (7 ppb). They also noted that the compounds Aroclor 1242 and Aroclor 1254 were more toxic to phytoplankton than were the pure compounds, DDT or 2,4-D. Like Mosser et al. (1972), they noted that organochlorines are more acutely toxic in mixed cultures than in single species cultures.

Harding (1976) noted that phytoplankton photosynthesis may be affected by temporal and geographical differences due to variations in salinity, temperature, particulate composition, nutrient levels and phytoplankton community composition. In the northern Adriatic Sea, PCBs reduced phytoplankton photosynthesis at 10 ppb; the magnitude of reduction differed with region and season. In Long Island Sound, two species of *Thalassiosira* showed inhibited growth and photosynthesis following a single dose of 10 µg/liter PCB. However, within a few days, the rates of growth and photosynthesis equalled and surpassed those of the control signifying this species' ability to completely recover from PCB exposure. Inhibition of photosynthesis is believed to be due to reduced levels of chlorophyll-a per PCB-treated cell (Powers et al. 1977).

In this experiment, all cell sizes exhibited a reduction to 30 percent of the control biomass. Because a full recovery of biomass would require several days, in the natural environment this period of time may suffice for the less dominant, faster-growing and more resistant species to establish themselves, thereby changing community structure. Also, a period of days without these essential algae could have a negative impact on herbivore populations.

A study of Long Island Sound natural phytoplankton assemblages also showed a reduction and recovery of growth after exposure to PCBs at concentrations of 1 or 10 µg/day (O'Connors et al. 1978). Rate of recovery increased with higher concentrations. Unlike the above experiment, effects differed with cell size. Treatment of communities with one µg/liter PCB

affected particles larger than nine μm ESD for three days, but smaller particles were unaffected. Treatment with 10 μg/liter PCB suppressed small and large particles with a recovery of small particles within three days. Therefore, large diatoms are more sensitive to PCBs than are smaller diatoms. PCBs also favored smaller algae in a study of estuarine phytoplankton exposed to five or 10 μg/liter of Aroclor 1254 (PCB) (Biggs et al. 1978). These results further contribute to the possibility that organochlorines can affect species composition thereby altering entire oceanic food webs. Large phytoplankton forming short food chains tend to produce harvestable fish whereas small phytoplankton believed to produce longer food chains result in "ecosystems containing numerous ctenophores, jellyfish, and other gelatinous predators" (O'Connors et al. 1978).

Other chemicals which can affect the growth rate and carbon uptake of marine phytoplankton include chlordane (10μg/liter) (Biggs et al. 1978), Di-n-butyl Phthalate (Acey et al. 1987) and polynuclear aromatic hydrocarbons (Riznyk et al. 1987).

Effects of contaminants on freshwater algae are similar to marine plankton in that sensitivity and resistance differ with species. Up until the early 1980's most research was conducted on marine plankton, with the majority focusing on PCBs. Later research incorporated insecticide and herbicide effects on stream and lake communities.

The effect of PCBs on freshwater phytoplankton from oligotrophic and eutrophic lakes appears to be dependent on the density of plankton cells (Sodergren and Gelin 1983). This may be due to a threshold under which the level of PCBs accumulated per cell do not affect carbon fixation rates. Therefore, more resistant species are able to assimilate certain PCB concentrations with only a temporary decline in photosynthetic rate. Phytoplankton in an oligotrophic lake in Sweden were more sensitive to PCBs (26 μg/liter) than phytoplankton in eutrophic lakes since oligotrophic phytoplankton did not adapt 16 hours after addition of PCBs (26 μg/liter) than phytoplankton in eutrophic lakes since oligotrophic phytoplankton did not adapt 16 hours after addition of PCBs. A 70 percent reduction in carbon fixation rates occurred during the spring and a 57 percent reduction occurred during the summer (Sodergren and Gelin 1983). Further reduction was noted after 16 hours.

In contrast, eutrophic lake phytoplankton, following a large spring bloom of the diatom *Stephanodiscus hantzshii*, suffered a 15 percent reduction in primary productivity following PCB addition. Photosynthesis rates showed greater reduction during the autumn when phytoplankton biomass was smaller. Of the total amount of the 26 μg/liter PCBs added to the eutrophic lake phytoplankton samples, 46 percent was found in the algae during the spring and 30 percent in the autumn (Sodergren and Gelin 1983).

Transmission electron microscopy studies of algae ultrastructure following PCB exposure showed that the chloroplast is the organelle most sensitive to PCBs. *Chlorella fusca* var. vacuolata, *Scenedesmus quadricauda*, and *Scenedesmus obliquus* all showed disruption of the chloroplast after a 48 hour exposure to one μg/ml of PCB (Mahanty et al. 1983). These results suggest that PCB sensitive phytoplankton experience a reduction in photosynthetic rates due to irreversible damage to their chloroplasts. Geike and Parasher (1978) have shown that 5.0 ppm

of HCB causes a 50 percent inhibition of photosynthesis in the alga *Chlorella pyrenoidosa* also because of changes in ultrastructure; 33.3 percent inhibition was noted at 0.1 ppm HCB and 42 percent at 1.0 ppm HCB.

Research on metals from atmospheric deposition and other sources has shown effects including changes in plankton community structure and significant decreases in primary production (Rybak et al. 1989). A 14 year study of a lake receiving waste from a heavy metal mine uncovered the extinction or severe rarity of desmid and diatom species (Austin and Munteanu 1984). Evidence therefore exists of possible perturbation of aquatic food chains through substances other than pesticides or industrial chemicals.

Thus, the degree of effect of chemical exposure to marine and freshwater plankton is highly dependent on species (due to natural variances in sensitivity in genotypes), chemical mixture, and nutrient availability. Research indicates that pesticides and metals cause a reduction in primary production, however, this effect is usually temporary and does not occur at the community level. A more important consequence of chemical exposure is the alteration of the aquatic food chain, on a short- or long-term basis. The complete or partial loss of sensitive species can cause a shift in plankton community structure and composition which can potentially alter an entire food chain, with repercussions which are yet undefined. Tinkering with the very base of an ecosystem's food web could cause shifts in predator/prey ratios and relationships throughout trophic levels thereby changing the composition of food sources in the highest echelons of the food chain. Although most of the studies described above were conducted with concentrations higher than those presently recorded in the environment, the absorption and uptake of many of these chemicals by plants and live and dead plankton alike undermines the levels recorded in water from streams and lakes.

Effects of these pollutants on humans and aquatic life are all considered to be from chronic exposure. There are no known instances of acute toxic effects of these compounds in any of the Great Water regions.

The populations at risk from exposure to these compounds include the top predators in the aquatic food webs (e.g., sport fish); fish-eating wildlife (e.g., mink (*Mustela vison*), eagles, gulls, terns, etc.); and human populations which consume large quantities of fish from Great Waters areas (e.g., commercial fishermen and families, charter boat operators and families, subsistence anglers such as Vietnamese, Native Americans) children, older people, and women of childbearing age (concern for fetal exposure).

2.2.3.4 Biological Effects of Compounds of Concern

A number of chemicals transported atmospherically to water bodies are affecting the health of wildlife and humans. Few of these chemicals are acute toxicants, powerful human carcinogens, or genotoxicants at ambient concentrations (Colborn 1989). However, they are developmental toxicants capable of altering the formation and function of critical physiological

systems and organs. Thus, the developing embryo, fetus, and breast feeding offspring are particularly sensitive to these chemicals (Table 8). This section summarizes the deleterious effects of these contaminants on development, function, reproductive potential, behavior, and disease processes in animals and humans as a result of exposure associated with freshwater and marine resources. Each effect will be discussed in detail in the following sections covering the discrete and multiple impacts of these compounds of concern.

Residues of the chemicals of concern have been reported in human tissue (Table 9), including reproductive tissue (Table 10). For some of the chemicals an association has been made between body burdens of the chemicals for those who regularly include fish in their diet (Table 11). Mykkanen and coworkers (1986) estimated that 1 percent of daily energy, 1 percent of daily cadmium, and 37 percent of daily mercury intake is from fish in the diet of Finnish children.

Two of the atmospherically transported compounds of concern are not toxic substance, but rather, are nutrients. Nitrogen and phosphorus are of concern because of their impacts on the eutrophication of estuaries and freshwaters, respectively. The effects of these compounds will be considered separately under the heading "Eutrophication". The effects of toxic compounds will be discussed in the sections entitled "Cancer, "Immune System Impairment", "Metabolic Impairment", "Nervous and Behavioral Impairment", "Endocrine Disruption", "Reproductive Impairment" and "Transgenerational Effects".

Under ideal circumstances, an investigation into the quality of the data for each study utilized in the preparation of a review manuscript would be made. Such data quality review is obviously beyond the scope of this effort. However, a series of decisions made prior to the inception of this project serve to establish relative confidence in the data used.

The studies and the information used in the preparation of the various sections of this document are the most currently available data. Every effort has been made to restrict the use of older studies to the role of comparison with contemporary data. In most cases, the older studies have been utilized to either compare or contrast the older evidence with current contributions and new knowledge. Further, efforts were made not to incorporate a single study indicating a unique endpoint, and to present it in the absence of supporting information. Whenever possible, supporting studies have also been incorporated and discussed. In this fashion, the question of individual data quality within a single study is minimized, and a relative degree of confidence in the complete data set presented can be achieved.

FIGURE 4

ROUTES OF TCDD EXPOSURE FOR HUMANS

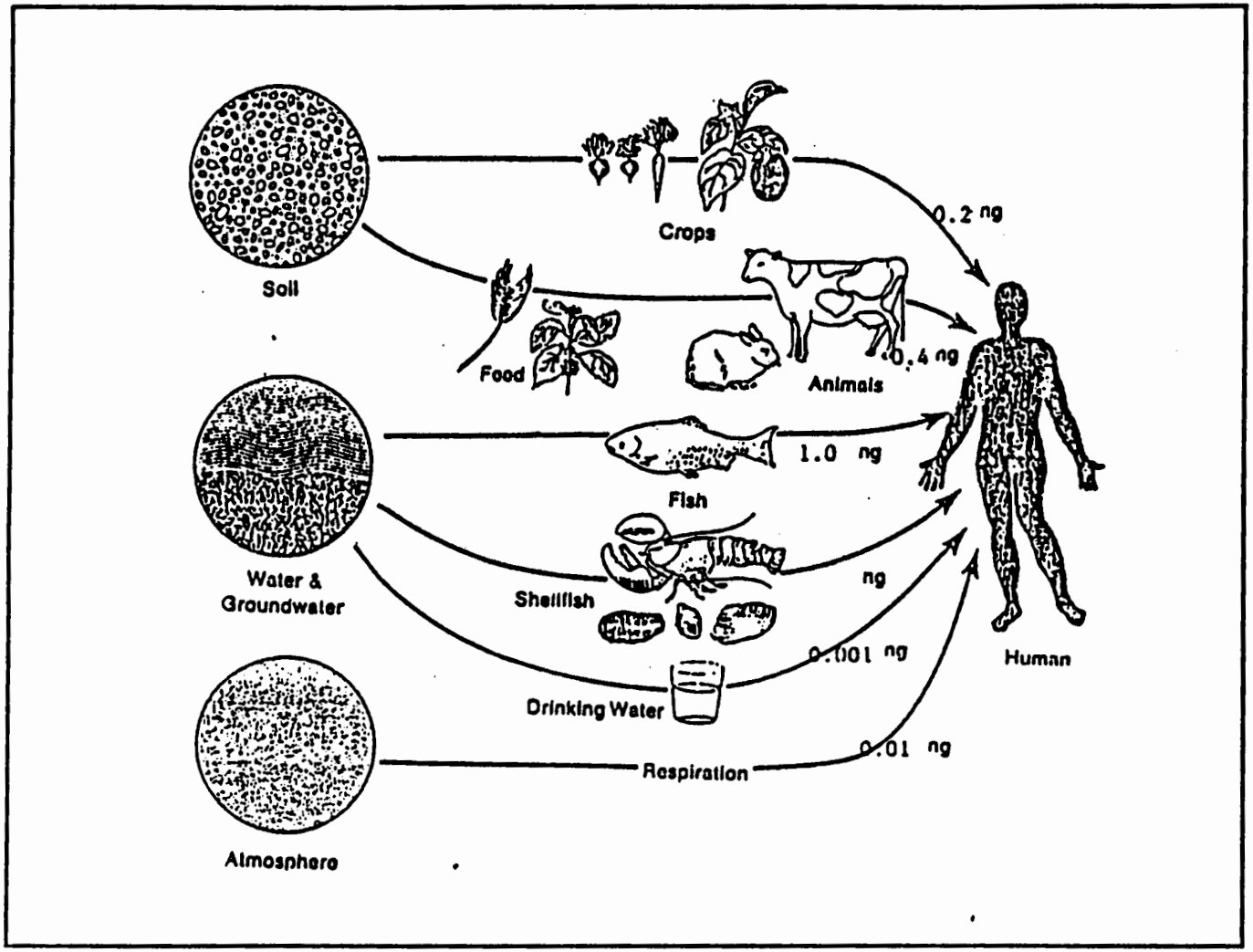


TABLE 8

POPULATIONS AT RISK FROM EXPOSURE TO TOXIC POLLUTANTS

POPULATION AT RISK
piscivorous fish
fish–eating wildlife and birds
commercial fishermen
charter boat operators
subsistence fish eaters
children
elderly
women of childbearing age

TABLE 9

EFFECTS OF COMPOUNDS OF CONCERN IN HUMANS

Compound	Genotoxic	Carcinogenic	Reproductive Effects	Developmental Effects	Immunotoxic	Neurological Effects	Target Organ Damage	Accumulated in Human Tissues
2,3,7,8-TCDD (Dioxin)	E ATSDR 1987	0	0	E Erickson et al. 1984	E ATSDR 1987	E Barbieri et al. 1988, Levy 1988	+ ATSDR 1987	+ Jensen 1987
Benzo[a]pyrene (B[a]P)	0 ATSDR 1987	E ATSDR 1987	0	0	0	0	0	0
Cadmium (Cd)	0 ATSDR 1987	+ Kazantzis et al. 1988	0	E Bonithon-Kopp et al. 1986a	0	0	+ ATSDR 1987	+ Piscator 1985, Subramanian et al. 1985
Chlordane	0	0 IARC 1986	0	0	0	+ USEPA 1985, ATSDR 1988	0	+ Taguchi & Yakushiji 1988
DDT/DDE	– Cabral 1985	0 Falck et al. 1992	0	0	0	+ WHO 1979	0	+ Williams et al. 1988, Davies & Mes 1987
Dieldrin	0 ATSDR 1987	E ATSDR 1987	0	0	E ATSDR 1987	+ ATSDR 1987	0	+ Williams et al. 1988

TABLE 9 (Cont.)

Compound	Genotoxic	Carcinogenic	Reproductive Effects	Developmental Effects	Immunotoxic	Neurological Effects	Target Organ Damage	Accumulated in Human Tissues
HCB	0	0	+ USEPA 1987	+ USEPA 1987	0	+ USEPA 1987	+ USEPA 1987	+ Williams et al. 1988
Lead (Pb)	E EPA, 1989	+ IARC 1986 EPA, 1989	+ ATSDR 1988 EPA 1986, 1990	+ ATSDR 1988 EPA 1986, 1990	E ATSDR 1988 EPA 1986, 1990	+ ATSDR 1988 EPA 1986, 1990	+ ATSDR EPA 1986, 1990	+ Subramanian et al. 1985
Lindane	0	0 IARC 1986	0	0	0	0	0	+ Mes et al. 1977, Davies & Mes 1987
Mercury (Hg)	E ATSDR 1988	0 USEPA-ODW 1987	0	E Nordberg 1988	E WHO 1976	+ WHO 1976	+ Nordberg 1988, Grubb et al. 1987	+ Subramanian et al. 1985
Mirex	0	0	0	0	0	0	0	+ Williams et al. 1988
PCB	0	E ATSDR 1987	E ATSDR 1987	+ ATSDR 1987	E Shigematsu et al. 1978, Chang et al. 1980	0	0	+ Williams et al. 1988, Humphrey 1983
Toxaphene	E WHO 1984	0	0	0	0	+ WHO 1984	0	0

Legend:
0 = No information
E = Equivocal
+ = Positive results
− = Negative results

A zero (0) does not necessarily mean there is no effect; it can also mean that no studies have been done.

TABLE 10

COMPOUNDS OF CONCERN FOUND IN HUMAN REPRODUCTIVE TISSUE

COMPOUND	OVARIAN FOLLICLE	PLACENTA	TESTICLE
Cadmium		Korpel et al. 1986	
Chlordane (HE)	Baukloh et al. 1985, Trapp et al. 1984		Szmcynski & Waliszewski 1981
DDE/DDT	Trapp et al. 1984, (DDT) Baukloh et al. 1985		Dougherty et al. 1980, Szmcynski & Waliszewski 1981, (DDE) Bush et al. 1986, Schecter et al. 1989
Dieldrin	Trapp et al. 1984, Baukloh et al. 1985	USPHS-ATSDR 1987	
HCB	Trapp et al. 1984	Ando et al. 1985 Courtney and Andrews 1985	Szmcynski & Waliszewski 1981, Dougherty et al. 1980, Bush et al. 1986, Schecter et al. 1989
Hg		Capelli and Minganti 1986 Kuhnert et al. 1981	
Lead		Korpela et al. 1986 Kuhnert & Kuhnert 1988	
Lindane (g-HCH)	Trapp et al. 1984, Baukloh et al. 1985		Szmcynski & Waliszewski 1981
(a-HCH)	Trapp et al. 1984, Baukloh et al. 1985		Szmcynski & Waliszewski 1981
(b-HCH)	Trapp et al. 1984, Baukloh et al. 1985		Szmcynski & Waliszewski 1981
Mirex			Bush et al. 1986
PCB	Trapp et al. 1984, Baukloh et al. 1985	Ando et al. 1985	Dougherty et al. 1980, Bush et al. 1986, Schecter et al. 1989
2,3,7,8-TCDD			Schecter et al. 1992

TABLE 11

RESIDUES REPORTED IN HUMANS THAT SHOW AN ASSOCIATION WITH THOSE WHO REGULARLY INCLUDE FISH IN THEIR DIET

Chlordane	Wariishi et al. 1986
DDE	Wisconsin DOH 1987, Rogan et al. 1986a, Kanja et al. 1986, Bush et al. 1984, Noren 1983, Kreiss et al. 1981
HCB	Noren 1983
Lead	Dabeka et al. 1986
Lindane	Sloof and Matthijsen 1988
Mercury	Langworth et al. 1988, Wisconsin DOH 1987, Mykkanen et al. 1986[1], Lommel et al. 1985
2,3,7,8–TCDD	Schecter et al. 1990
Mirex	WHO 1984
OCS	Lommel et al. 1985
PCB	Jacobson and Jacobson 1988, Wisconsin DOH 1987, Humphrey 1985, Bush et al. 1984, Schwartz et al. 1983, Jensen and Slorach 1991

[1] Mykkanen et al. 1986. Estimated one percent of daily energy; one percent of daily Cd; and 37 percent of daily Hg intake are from fish.

2.2.4 Ecosystem Level Effects of Toxic Substances

The biological effects of pollution can occur at a variety of levels of biotic organization, from the subcellular to whole populations and ecosystems. The science relating effects of toxic substances across these biotic scales is not well developed, and it is often quite difficult to state precisely how an effect on the physiology of an organism or on cellular processes will be expressed (if at all) at the scale of populations or ecosystems. Often, scientists are unable to predict with any certainty because population numbers may be controlled largely by processes other than reproduction -- such as the survival of fish larvae in the face of a high predation pressure or the extent of energy flow to the fish population up the food web. This does not imply that populations and ecosystems are better buffered against the effects of toxic substances than are lower levels of biotic organization (cells, organs, organisms), rather it suggests only that there is great uncertainty in understanding the relationships among levels.

The effects of toxic substances on populations and ecosystems have received far less study than have effects on individual organisms. However, recent reviews (Schindler 1987; Howarth 1991) have reached some general conclusions: changes in the structure of a community are a more sensitive indicator of toxic stress than are changes in ecological processes such as primary production; indirect effects resulting from subtle changes in competition and food web structure can have major ramifications on populations and aquatic ecosystems; and unexpected effects from pollution are commonly found in pollution studies.

Two examples can illustrate the complexity of the response of aquatic ecosystems to stress. Whole-lake experiments at Canada's experimental lakes area showed that the major effect of acidification on fish is an indirect one. While extreme acidification in these experiments resulted in loss of trout without mobilization of aluminum by altering the structure of the food web. The trout gradually starved and were unable to reproduce (Schindler et al. 1985).

In another example, an oil spill in the Baltic Sea resulted in decreased hatching success of herring eggs, but the effect was not a result of direct toxicity on the eggs. Laboratory studies showed a high tolerance of these fish eggs to oil. Rather the effect of the oil was to kill off benthic amphipods, and the loss of the amphipods resulted in a fungal overgrowth of the fish eggs, killing many of them. Normally, the amphipods graze upon the fungi and keep it under control (Nellbring et al. 1980).

Thus, the state of present knowledge of the effects of toxic substances at the ecosystem level is inadequate. Future research efforts will be required to enable an understanding of the potential alterations in relationships among the various levels of ecosystem organization.

2.2.5 Discrete Effects of Contaminants of Concern

2.2.5.1 Eutrophication

Eutrophication was recognized as a major problem in the Great Lakes and many estuaries at least 30 years ago (Ryther 1954; Davis 1964; Beeton 1965; Ryther and Dunstan 1971; E.P.A. 1971). During the 1970's, management steps were taken to reduce the inputs of phosphorus to the Great Lakes. As a result, Lakes Erie and Ontario have substantially recovered from eutrophication (DePinto 1986; Lean 1987; Schindler 1987; DePinto 1991; Schelske and Hodell 1991). There has also been progress in reducing eutrophication in some limited estuarine areas as well, such as coastal ponds on Long Island which were affected by runoff from duck farms in the 1950's (Ryther 1989) and Kaneohe Bay in Hawaii which received large sewage inputs until the mid 1970's (Smith 1981). However, in general, the problem of eutrophication in estuaries has grown (Office et al. 1984; Larsson et al. 1985; Rosenberg 1985; D'Elia 1987; Baden et al. 1990; Parker and O'Reilly 1991; Lein and Ivanov 1992; Jaworski et al. 1992). Recently, eutrophication was identified as the most serious pollution problem facing the estuarine waters of the United States (NRC 1993).

The principal reason for the slower remediation of estuarine waters is that, while eutrophication in lakes is controlled by phosphorus, nitrogen controls eutrophication in most temperate-zone estuaries. More effort has been expanded to control phosphorus, and the sources of nitrogen are more diffuse and difficult to control (Butt 1992). As a result, many estuaries receive nitrogen inputs per unit area which are more than 1,000-fold greater than those of heavily fertilized agricultural fields (Nixon et al. 1986). In moderation, nitrogen inputs to estuaries and coastal seas can be considered beneficial, since they result in increased production of phytoplankton (the microscopic algae floating in water), which, in turn, can lead to increased production of fish and shellfish (Nixon 1988; Rosenberg et al. 1990; Hansson and Rudstam 1990). Excess nitrogen can be highly damaging, leading to effects such as anoxia and hypoxia from eutrophication, nuisance algal blooms, dieback of seagrasses and corals, and reduced populations of fish and shellfish (Ryther 1954, 1989; Kirkman 1976; McComb et al. 1981; Kemp et al. 1983; Officer et al. 1984; Gray and Paasche 1984; Cambridge and McComb 1984; Larsson et al. 1985; Price et al. 1985; Rosenberg 1985; D'Elia 1987; Rosenberg et al. 1990; Cederwall and Elmgren 1990; Baden et al. 1990; Hansson and Rudstam 1990; Parker and O'Reilly 1991; Lein and Ivanov 1992; Smayda 1992). Eutrophication also may change the plankton-based food web from one based on diatoms toward one based on flagellates or other phytoplankton which are less desirable as food to organisms at higher trophic levels (Doering et al. 1989).

In most estuaries, the sources of nitrogen are only poorly known. However, atmospheric sources can be important, in sharp contrast to phosphorus inputs, for which air borne pathways are generally quite minor (Wolfe et al. 1991; Jaworski et al. 1992). Inputs of nitrate and ammonium directly to the surface waters of Long Island Sound from the atmosphere are estimated to be at least 10 percent of the total nitrogen inputs (Wolfe et al. 1991). However, indirect inputs of nitrogen from airborne sources are probably much larger, since over half of the nitrogen comes from upstream sources and urban runoff (Wolfe et al. 1991). Studies of the

watersheds of the entire Chesapeake Bay (Fisher and Oppenheimer 1991) and of the upper Potomac River (Jaworski et al. 1992) have suggested that 28 percent and 40 percent, respectively, of the nitrogen fluxes into the watershed come from atmospheric deposition. Not all of the nitrogen deposited on a watershed flows downstream to an estuary; studies in several watersheds near Chesapeake Bay have suggested that roughly two thirds of the nitrogen deposition falling on forested lands is retained in the forest (Groffman and Jaworski 1991; Jaworski et al. 1991). The factors controlling nitrogen retention by forests are poorly known, but uptake by trees is probably a major mechanism (Jaworski et al. 1991) since many forests are nitrogen limited (Vitousek and Howarth 1991). However, fully mature forests presumably will not retain as much nitrogen because there is no net growth of trees (Jaworski et al. 1991). Further, if sufficient nitrogen is added to a forest via deposition, the forest can become nitrogen "saturated" (Aber et al. 1991). Increasing concentrations of nitrate in streams in the Catskill Mountains of New York over the past decade suggest that the forests there have become saturated and are now exporting more nitrogen downstream (Murcoh and Stoddard 1991).

Nutrient Limitation

Nitrogen and phosphorus are essential nutrients for plant growth. Phytoplankton production in most lakes, coastal marine ecosystems, and estuaries is nutrient limited. As a result, increased nutrient inputs lead to higher production and eutrophication (Edmondson 1970; Ryther and Dunstan 1971; Vollenwieder 1976; Schindler 1977, 1978; Schindler et al. 1978; Graneli 1978, 1981, 1984; McComb et al. 1981; Boynton et al. 1982; Nixon and Pilson 1983; Wetzel 1983; Valiela 1984; Smith 1984; Nixon et al. 1986; D'Elia et al. 1986; D'Elia 1987; Howarth 1988; Andersen et al. 1991). Unfortunately, the discussion of nutrient limitation in aquatic ecosystems has been surrounded by some confusion, in part because the term can have many different meanings and is often used quite loosely (Howarth 1988). Further, potential methodological problems in determining nutrient limitation increase the confusion (Hecky and Kilham 1988; Howarth 1988; Banse 1990). In the case of eutrophication, the appropriate definition of nutrient limitation is the regulation of the potential rate of net primary production by phytoplankton (Howarth 1988). Net primary production is defined as the total amount of photosynthesis minus the amount of plant respiration occurring in a given area (or volume) of water in a given amount of time. If an addition of nutrients would increase the rate of net primary production -- even if such an addition means a complete change in the species composition of the phytoplankton, production is considered to be nutrient limited (Howarth 1988; Vitousek and Howarth 1991).

Factors other than nutrient input can also influence or partially control primary production. For example, phytoplankton production in some estuaries (e.g., the Hudson River) is limited by light availability. Such light limitation tends to occur in extremely turbid estuaries, or in estuaries which moderate turbidity coexists with deep mixing of the water. The turbidity can result both from suspension of inorganic particles and from high phytoplankton biomass. Thus, light limitation often is a result of self-shading by the phytoplankton (Wetzel 1983). In estuaries where nutrient inputs are high and production is limited by light, the nutrients are simply transported further away from the source before being assimilated by phytoplankton, e.g., the

Hudson River and New York Harbor into the New York Bight (Malone 1982). This transport may or may not provide sufficient dilution to avoid excessive eutrophication. Frequently, eutrophication simply occurs further afield from the nutrient source.

Zooplankton and other animals can influence the rate of primary production and the biomass of phytoplankton by their grazing on phytoplankton. This phenomenon has received extensive study and discussion in both freshwater ecosystems (Carpenter et al. 1985, 1987; Morin et al. 1991), and in offshore ocean ecosystems (Steele 1974; Banse 1990). However, the effects of grazing are largely unstudied in estuaries and coastal seas (Rudstam et al. 1992). In lakes, higher abundances of phytoplankton and higher rates of net primary production occur when zooplankton biomass is lower (Carpenter et al. 1987; Morin et al. 1991). Changes in the abundance and species composition of fish (Carpenter et al. 1985) and of filter-feeding benthic organisms may also affect phytoplankton abundance. For instance, water clarity in Lake Erie has increased greatly after the unintentional introduction of zebra mussels (E. Mills 1992, personal communication). In general nutrient supply should be viewed as the cause of eutrophication, with grazing pressures being a secondary regulator.

Nitrogen Versus Phosphorus Limitation

In the 1960's and early 1970's, there was intense debate over which nutrient controlled eutrophication in lakes (see papers in the volume edited by Likens 1972). By the late 1970's, however, phosphorus inputs were clearly identified as the major factor, at least in mesotrophic and eutrophic lakes (Vollenwieder 1976; Schindler 1977, 1978; Schindler et al. 1978; Wetzel 1983). As a result, management strategies were undertaken to reduce phosphorus inputs into the Great Lakes. These strategies have been successful and, in response, these lakes recovered from eutrophication during the 1980's (DePinto 1986; Lean 1987; Schindler 1987; DePinto 1991; Schelskè and Hodell 1991).

In contrast to the Great Lakes and most other temperate-zone lakes, nitrogen is probably the element usually limiting to primary production by phytoplankton in most estuaries and coastal seas of the temperate zone (Ryther and Dunstan 1971; Vince and Valiela 1973; Smayda 1974; Norin 1977; Graneli 1978, 1981, 1984; Boynton et al. 1982; Nixon and Pilson 1983; Valiela 1984; Nixon et al. 1986; D'Elia et al. 1986; Howarth 1988; Frithsen et al. 1988; Rydberg et al. 1990; Vitousek and Howarth 1991; Nixon 1992). However, some temperate estuaries such as the Apalichicola in the Gulf of Mexico may be phosphorus limited (Myers and Iverson 1981; Howarth 1988) and others, e.g., parts of Chesapeake Bay and the Baltic Sea, may switch seasonally between nitrogen and phosphorus limitation (McComb et al. 1981; D'Elia et al. 1986; Graneli et al. 1990; Andersen et al. 1991). Many tropical estuarine lagoons also may be phosphorus limited (Smith 1984; Smith and Atkinson 1984; Howarth 1988; Vitousek and Howarth 1991).

The question of nitrogen limitation of primary production in most temperate-zone estuaries and coastal seas was much debated throughout the 1980's (D'Elia 1987; Howarth 1988; Nixon 1992). One argument against nitrogen limitation was that phosphorus is generally limiting

in temperate-zone lakes and, until recently, there was little evidence that the biogeochemical processes regulating nutrient limitation were fundamentally different in freshwater as compared with marine ecosystems (Schindler 1981; Smith 1984). Another argument was that much of the evidence for nitrogen limitation in marine ecosystems came from extremely short-term, small-scale enrichment experiments in flasks or bottles. It may not be possible to extrapolate the results of such short-term enrichment experiments to an entire ecosystem (Smith 1984; Hecky and Kilham 1988; Howarth 1988; Marino et al. 1990; Banse 1990).

In recent years, increasing evidence has accumulated indicating that nitrogen is limiting in many coastal marine ecosystems, and that the biogeochemical processes regulating nutrient limitation do vary between marine and freshwater ecosystems. The new evidence for nitrogen limitation consists of generally low concentrations of dissolved nitrogen compared with dissolved phosphorus (Boynton et al. 1982; Graneli 1984; Valiela 1984) and longer, large-scale enrichment experiments (D'Elia et al. 1986), including one mesocosm experiment of many months duration (Frithsen et al. 1988; Nixon 1992; Frithsen et al., unpublished data). While any one such piece of evidence may not be entirely convincing, the good agreement among the several studies convincingly demonstrates nitrogen limitation (Howarth 1988; Vitousek and Howarth 1991).

At least three factors in the biogeochemical cycles appear important to the question of nitrogen or phosphorus limitation: (1) the ratio of nitrogen to phosphorus in nutrient inputs to estuaries is frequently less than for lakes, (2) the sediments are often a more important sink of phosphorus in lakes than in marine ecosystems, and (3) nitrogen fixation is a more prevalent process in the plankton of lakes (Howarth 1988). Each of these differences is discussed briefly below.

(1) In both freshwater and marine ecosystems, the relative requirements of phytoplankton for nitrogen and phosphorus are fairly constant, with the two elements being assimilated in the approximate molar ratio of 16:1 (Redfield 1958). If there were no biogeochemical processes acting within a water body, the ratio of nitrogen to phosphorus in the nutrient inputs to the ecosystem would determine whether the system were nitrogen or phosphorus limited, with ratios below 16:1 leading to nitrogen limitation and higher ratios leading to phosphorus limitation (Howarth 1988). In fact, the N:P ratios in nutrient loadings to many estuaries and coastal seas are below this ratio, while nutrient inputs to temperate lakes tend to have higher N:P ratios (Jaworski 1981; Kelly and Levin 1986; NOAA/EPA 1988). This difference in ratios probably reflects the relative importance of sewage, which tends to have a low N:P ratio, as a nutrient source of coastal waters.

(2) Biogeochemical processes within sediments act to alter the relative abundance of nitrogen and phosphorus in an ecosystem. Denitrification, the bacterial reduction of nitrate to molecular nitrogen, removes nitrogen and tends to make coastal marine ecosystems more nitrogen limited (Nixon et al. 1980; Nixon and Pilson 1983). However, this process appears to be even more important in lakes than in estuaries and coastal seas; a higher percentage of the nitrogen mineralized during decomposition is denitrified in lake

sediments than in estuarine sediments (Seitzinger 1988; Gardner et al. 1991; Seitzinger et al. 1991). Of more importance in explaining a tendency for nitrogen limitation in coastal marine ecosystems of the temperate zone, therefore, is the relatively high phosphorus flux from sediments; nutrient fluxes from these sediments have fairly low N:P ratios (Rowe et al. 1975; Boynton et al. 1980; Nixon et al. 1980). In many lakes, phosphorus is bound in the sediments (Schindler et al. 1977), although in others, phosphorus fluxes are comparable to marine sediments (Khalid et al. 1977). Nutrient fluxes from lake sediments can be either enriched or depleted in nitrogen relative to phosphorus (Kamp-Nielsen 1974). Caraco et al. (1989, 1990) have suggested that the abundance of sulfate in an ecosystem partially regulates the sediment flux of phosphorus, with phosphorus binding in sediments being greatest where sulfate concentrations are lowest. This suggestion is consistent with variable fluxes in lakes and higher fluxes in coastal marine ecosystems.

(3) When the relative abundance of nitrogen to phosphorus is low in the water column of lakes, nitrogen-fixing species of cyanobacteria are favored since they can convert molecular nitrogen to ammonium or organic nitrogen. Under such nitrogen-depleted conditions in lakes, these cyanobacteria often are the dominant phytoplankton species and fix appreciable quantities of nitrogen. As a result, nitrogen deficits (relative to phosphorus) can be alleviated, and primary production in the lake is phosphorus limited (Schindler 1977; Flett et al. 1980; Howarth 1988; Howarth et al. 1988a). In contrast, nitrogen-fixing cyanobacteria are rare or absent from the plankton of most estuaries and coastal seas, a condition helping to maintain nitrogen limitation in these ecosystems (Howarth 1988; Howarth et al. 1988a). Exceptions are found in the Baltic Sea (Lindahl and Wallstrom 1985) and in the Australian Harvey-Peel estuary (McComb et al. 1981), but are unknown in the waters of the U.S. The explanation for the rarity of planktonic, nitrogen-fixing cyanobacteria in coastal marine waters is still subject to debate (Howarth et al. 1988b; Paerl et al. 1987; Paerl and Carlton 1988; Carpenter et al. 1990; Marino et al. 1993). Possible reasons include one or more of the following: a lower availability of iron and molybdenum required for nitrogen fixation in saline water (Howarth and Cole 1985; Howarth et al. 1988b; Marino et al. 1990), greater turbulence in coastal marine systems, allowing oxygen to poison the nitrogenase enzyme responsible for nitrogen fixation (Paerl et al. 1987; Paerl and Carlton 1988); greater grazing pressure on cyanobacteria in marine systems (Vitousek and Howarth 1991); and a lower light availability in estuaries and coastal waters due to higher turbidity and/or deeper mixed layers (Howarth and Marino 1990; Vitousek and Howarth 1991).

As noted above, many tropical estuaries and coastal systems may be phosphorus limited (Smith 1984; Smith and Atkinson 1984). Although the evidence for limitation of production by phytoplankton is not entirely clear in tropical systems (Howarth 1988), and production by seagrasses and attached macroalgae is sometimes nitrogen limited in tropical systems (Lapointe et al. 1987; McGlathery et al. 1992), primary production by seagrasses in many tropical areas is clearly limited by phosphorus (Short et al. 1985; 1990; Littler et al. 1988; Powell et al. 1989). Phosphorus limitation in these systems is probably the result both of a high degree of phosphorus

adsorption in the calcium–carbonate sediments which dominate such tropical systems (Morse et al. 1985) and the high rates of nitrogen fixation associated with benthic algal mats and with symbionts of seagrasses in clear, relatively oligotrophic lagoons (Howarth 1988; Howarth et al. 1988a).

2.2.5.2 Cancer

None of the airborne compounds of concern are documented carcinogens in humans at ambient concentrations. However, occupational exposure to cadmium (Kazantzis et al. 1988), dioxin (Fingerhut et al. 1991; Manz et al. 1991) and B(a)P (ATSDR 1987) has been correlated with cancer. Falck et al. (1992) found elevated levels of PCB, DDT, and DDE in fatty breast tissue from women with breast cancer compared with breast tissue from women with non–malignant breast disease.

Other than reports on dermal and liver cancers in fishes and the beluga whales (*Delphinapterus leucas*) in the St. Lawrence River and Estuary, reports of cancer in wildlife are rare. In each of these cases the causal agents were discovered to be polyaromatic hydrocarbons (PAHs) in follow–up laboratory studies (Black et al. 1981; Black et al. 1982; Baumann and Harshbarger 1985; Hayes et al. 1987; Cairns and Fitzsimmons 1987; NOAA 1991).

High incidences of liver neoplasms in fish from highly contaminated sites in Puget Sound, Washington, have been reported along with assorted preneoplastic and regenerative lesions in English sole (*Parophrys vetulus*), rock sole (*Lepidopsetta bilineata*), and starry flounder (*Platichthys stellatus*) (NOAA 1991). Field and laboratory studies linked contaminant exposure not only to the liver neoplasms/lesions, but also to other metabolic effects. Sediments and PAHs extracted from sediments from contaminated harbors applied dermally and fed to fish induced dose–related tumors in the confined fish. Other fish species exhibiting similar lesions include the black croaker, flathead sole (*Hippoglossoides elassodon*), hardhead catfish, white croaker (*Genyonemus lineatus*), white perch (*Morone americana*), windowpane flounder, and winter flounder (*Pseudopleuronectes americanus*) (NOAA 1991).

Follow–up long–term field studies at other US locations supported the Puget Sound findings (Varanasi 1989). A high prevalence of liver lesions and/or neoplasms was found in starry flounder, black croaker, and winter flounder in San Francisco Bay, the Oakland Estuary, San Diego Bay, and the North East coast, respectively. Boston Harbor, East Raritan Bay, and Salem Harbor, all contaminated with aromatic hydrocarbons and PCBs, had winter flounder with high liver contaminant concentrations associated with liver neoplasms. Great Lakes studies revealed that epidermal papillomas, liver lesions, and a tumor were induced by topical or dietary exposure of bullheads to Buffalo River and Black River sediments (MacCubbin et al. 1985; Baumann et al. 1987; Black et al. 1985).

In the Chesapeake Bay ecosystem, liver neoplasms and other lesions were found in the mummichog (*Fundulus heteroclitus*) from Elizabeth River sites (Vogelbein et al. 1990) and 15

percent of the white perch from 15 estuarine tributaries (May et al. 1988). Ninety-three percent of the fish from the contaminated Elizabeth River site had visible hepatic lesions; thirty-three percent had hepatic carcinomas. Vacuolized liver cells were found in striped bass (*Morone saxatilis*) and other fish of the Choptank River, the Chesapeake and Delaware (C&D) Canal, the Potomac River near Quantico, and upper bay at the Susquehenna (Hall et al. 1987, 1988a, b). In addition, renal lesions were found in increased frequencies in Elizabeth River fish (Thiyagarajah et al. 1989) and in yearling striped bass from the Potomac River (Hall et al. 1987). Gill hypertrophy and gill lesions were also found in fish species exposed to water from the Elizabeth River, C&D canal sites, and the Potomac River (Hargis and Zwerner 1988; Hall et al. 1987; Hall et al. 1988b). Further, cataracts in spot, Atlantic croakers (*Micropogonias undulatus*), weakfish, spotted hake, and gizzard shad, as well as fin erosion in toadfish were attributed to benzo-a-pyrene in the Elizabeth River (Hargis and Zwerner 1988; Huggett et al. 1987).

At the organismic level, populations of commercially and ecologically valuable fish species which spawn in the Chesapeake Bay watershed are declining, suggesting an environmental impact which affects the spawning grounds (fresh-water and tributaries) (Wright et al. 1992). The health disturbances exhibited by fish species of the Chesapeake Bay estuary cannot be correlated directly to any one chemical or heavy metal in the natural environment (Helz and Huggett 1987; Wright et al. 1992). Wright and coworkers (1992) analyzed patterns of similarity for acute and sublethal effects across species and found that, of the heavy metals, copper and mercury were the most acutely and chronically toxic; and that insecticides were of greater detriment to aquatic organisms than herbicides. PAHs in the Elizabeth River, as with the Puget Sound studies on the English sole, contribute to the observed neoplasms in fish (Wright et al. 1992). Direct correlation between toxic chemicals and metals and the health effects observed in the Chesapeake Bay wildlife remains incomplete due to limited information at the population and community level; interaction of physical conditions such as salinity, pH, and temperature; the presence of disease organisms; and predation, competition, and human involvement in population survival (Wright et al. 1992). However, the prevalence of health disturbances, the loss of species diversity in the Bay, and the gradient of effects matched with the gradient of contamination from urban to remote sites indicate a contribution to the effects from toxic chemicals (Wright et al. 1992).

A 40 percent incidence of tumors was discovered in stranded beluga whales (*Delphinapterus leucas*) in the St. Lawrence necropsied between 1983 and 1990 (Beland et al. 1992; Martineau et al. 1988, 1987, 1985). Although these studies were performed on dead animals, age distribution studies confirmed that they were representative of the live population. The tumors found in the 1987-1990 group affected multiple organs (mammary, pulmonary, intestinal, gastric, and thymus) and were reported as malignant, benign, and abdominal mass. Over a ten year period 46 percent of the belugas had at least one tumor (Beland et al. 1992). The chemical contaminant levels of the St. Lawrence belugas were significantly higher than in Arctic belugas for mercury, lead, total DDT, PCBs, and mirex. Benzo-a-pyrene (BaP) DNA-adducts in brains and livers were discovered in 8 of 9 belugas tested (Beland et al. 1992).

The following stages of carcinogenesis in fish have been described: (1) initiation of tumorigenesis through exposure to known carcinogens such as B(a)P found in sediments and suspended in the water column; (2) promotion of tumorigenesis by PCBs on initiated cells; and (3) decreased immune function resulting from concomitant exposure to organochlorine contaminants that are known immune suppressants (Black et al. 1981; 1982; Baumann and Harshberger 1985; Hayes et al. 1987; Cairns and Fitzsimmons 1987).

2.2.5.3 Immune System Impairment

Linking immune system impairment with exposure to a toxic chemical(s) has been confounded by the presence of natural agents such as viruses and other pathogens which exhibit comparable symptoms in humans and wildlife. Although a direct cause–effect linkage has not been established with regard to immune suppression and xenobiotics in wildlife, a body of evidence exists in laboratory studies which demonstrate xenobiotic effects on the immune system. This section presents field observations of reduced immunocompetence in animals carrying elevated contaminant body burdens. Laboratory evidence of immunological changes in the presence of the same contaminants is also presented.

Wildlife Studies

Since 1987, an increased number of marine mammal mortality events and strandings have occurred in the Northern Hemisphere (Table 12). Dead or dying seals, dolphins, porpoises, and whales have been observed from the Pacific Northwest to the eastern coast of the U.S., the Gulf of Mexico, the Mediterranean Sea, and the Baltic and North Seas (Geraci 1989; Harwood et al. 1989; Lavigne and Schmitz 1990; Kuehl et al. 1991; Raga and Aguilar 1991; UNEP 1991; Sarokin and Schulkin 1992). General systemic infections, organ lesions, poor health, and inability to combat infection characterized animals in the die–offs. Factors suspected of contributing to the cause of death included newly discovered viral agents, called morbilliviruses, similar to canine distemper that are specific to seals or dolphins (Kuehl et al. 1991); climatic change resulting in a warmer environment conducive to the spread of contagious agents (Lavigne and Schmitz 1990); algal blooms producing neurotoxins, such as brevitoxin from red tide (Geraci 1989); and increased body levels of organohalogens (Raga and Aguilar 1991). Bottlenose dolphins from the Atlantic coast and striped dolphins from the Mediterranean Sea had liver, lung, and lymphatic system lesions. The liver lesions in striped dolphins and depleted lymphocyte follicles in bottlenose dolphins suggested chemical immunosuppression (Borrell and Aguilar 1991). In either case, the lesions could not be attributed to viral infection. Immunotoxic environmental agents were also cited as a possible cause of lymphoid depletion in pinnipeds on the southern California coast (Simpson and Gardner 1972; Cavagnelo 1979; Britt and Howard 1983). It is important to note that all of the affected marine species are toothed and dependent upon fish.

A ten year monitoring program revealed that the troubled population of beluga whales at the mouth of the St. Lawrence River hold significantly higher body burdens of PCBs, DDT, and

mirex than other declining marine mammal populations and the least contaminated, healthy population of Arctic beluga whales (Beland et al. 1991). Researchers suggested that general poor health, susceptibility to bacterial and viral infections, tumors, and other pathological abnormalities within the St. Lawrence population were the result of immunosuppressive activity of environmental contamination origin (Martineau et al. 1987; Muir et al. 1990; Beland et al. 1992). Beland (1992) determined that American eels are the vector for 100 percent of the mirex, 37 percent of the PCBs, 15 percent of the DDT in the St. Lawrence belugas. The migrating eels transport the material as they return from the Great Lakes to the Atlantic Ocean to spawn.

European field researchers tested the association between organochlorine chemicals and population decline in the harbor seal (*Phoca vitulina)* (Reijnders 1986; Brouwer et al. 1989). They found an association between PCBs and DDT and reproductive loss (see Section 2.2.5.7) and immune system function.

In the Chesapeake Bay ecosystem, biota have experienced similar impacts on their immune systems. Diminished immune response was demonstrated by decreased macrophage phagocytic activity in bottom-dwelling fish species of the Elizabeth River as compared with the York River (Warriner et al. 1988; Weeks and Warriner 1984; Weeks et al. 1986).

Saxena et al. (1992) found significant decreases in catfish (*Heteropneustis fossilis*) humoral immune response to the microorganism *Aeromonas hydrophila* resulted from low-level exposure to cadmium and hexachlorocyclohexane (HCH). Antibody titre, erythrocyte count, leukocyte count, hemoglobin, hematocrit, and total plasma protein were reduced significantly by the combination of HCH and cadmium. HCH and cadmium alone resulted in a significant reduction of erythrocytes, leukocytes, and hemoglobin. The effect seen with a combined exposure to cadmium and HCH indicated a synergistic immunosuppressive chemical action. Erdman (1983) found evidence of immune system impairment in Forster's and common terns (*Sterna hirundo*) experiencing a post-fledgling die-off in 1988.

Laboratory And Mechanistic Studies

The immune system is characterized by a highly responsive and integrated system of cells and tissues. The integrated nature of the immune system complicates and magnifies the effects of xenobiotics. The impairment of certain cells (such as helper T-cells) subsequently disrupts the function of other cells, such as cytotoxic T-cells and antibody-producing B-cells. The mechanism of immune-response impairment is best understood in the case of TCDD, although many of the effects of PCB are similar, and may operate through a similar mechanism. Relationships between sublethal exposure to PCBs, DDT, dieldrin, and dioxin and immune system dysfunction are substantiated by experimental studies (Tables 13 and 14).

Observations of significant impairment in both the cellular and humoral immune response to the chemicals of concern are as follows:

- susceptibility to viral and/or bacterial infection
- reduced antibody synthesis
- complement synthesis compromise
- thymic atrophy
- lymphoid depletion
- decreased macrophage, phagocyte, and bactericidal activity
- suppressed IgM response in offspring from maternal exposure.

TCDD is a potent immunosuppressant in laboratory animals (Sonawane et al. 1988; Holsapple et al. 1991). Effects include changes in innate and acquired immunity, including both humoral (antibody) and cell-mediated immune responses (Holsapple et al. 1991; Morris et al. 1991). The ED50 for suppression of plaque-forming cells (immunosuppression) of TCDD is 2.4 nmol/kg, and that of 2,3,4,7,8-PCDF, the most persistent and predominant congener found in human tissues, is 3.0 nmol/kg (Davis and Safe 1988).

Central to the immunosuppressive effects of xenobiotics are their effects on the major immune cell producing organs, the thymus and spleen. Reduction in thymic weight begins 4 days following administration of TCDD (Gorski et al. 1988), and will lead to eventual depletion of mature lymphocytes (Ivans et al. 1992). In birds, TCDD-induced immunodeficiency occurs by reducing the number of lymphoid cells in the bursa of Fabricius in a dose dependent manner (Nikolaidis et al. 1988).

TABLE 12

MAJOR MARINE MAMMAL DIEOFFS

COMMON NAME	SPECIES	YEAR	LOCATION	CITATION
Dolphin, bottlenose	*Tursiops truncatus*	1987–1991	Eastern Coast, Australia	Dayton 1991,
		1987–1988	North Atlantic, U.S.	Geraci 1989, Kuehl et al. 1991
		1990	Gulf of Mexico, U.S.	Lancaster 1990,
		1992	Matagora Bay, TX, U.S.	Potter 1992
Dolphin, striped	*Stenella coeruleoalba*	1990–1992	Mediterranean Sea	Raga and Aguilar 1992
Seal, Baikal	*Phoca sibirica*	1987–1988	Lake Baikal, Siberia	Simmonds 1991, UNEP 1991
Seal, grey	*Halichoerus grypus*	1987–1988	Baltic & North Seas, Europe	Harwood et al. 1989
Seal, harbor	*Phoca vitulina*	1987–1988	Baltic & North Seas, Europe	Dietz et al. 1989, Addison 1989
Seal, ringed	*Phoca hispada*	1987–1988	Baltic & North Seas, Europe	Oehme et al. 1990
Whale, beluga	*Delphinapterus leucas*	1979–1992	St. Lawrence Estuary, Canada	Beland et al. 1992
Whale, humpback	*Megaptera novaeangiea*	1987	North Atlantic, U.S.	Geraci 1989
Whale, sperm	*Physter macrocephalus*	1988–1990	European/Norwegian Coasts	Simmonds 1991

TABLE 13 (Cont.)

COMPOUND	CITATION	EFFECT
B[a]P	Bozelka and Salvaggio 1985	
	USPHS-ATSDR 1988	
	Myers et al. 1988	
Cadmium	Bozelka and Salvaggio 1985	
	USPHS-ATSDR 1988	
	Blakley 1988	
	Cifone et al. 1989	5 ng/ml to human lymphocytes dose dependent inhibition cell proliferation. Inhibits IL2 production and partially receptor expression.
Chlordane	Bozelka and Salvaggio 1985	
	Barnett et al. 1985*	
	Beggs et al. 1985	
	Johnson et al. 1987	
Chlordane	Blaylock et al. 1990	CTL and NK responses differ in adult offspring of mice fed peanut butter prenatally 0, 4, or 8 mg/day/b.w depending on age and sex.
	Menconi et al. 1988	<1 $\mu g/m^3$ to > 5 $\mu g/m^3$ dose-response relationship with sinusitis, bronchitis, and migraine in residents in homes treated.
DDT/DDE	Kaminski et al. 1986	Macrophages *in vitro* exhibited significant phagocytotic ability.
	Banerjee et al. 1986, 1987 a, b	Altered cell-mediated responses, decreased IgM-antibody production in rodents.

TABLE 13

TOXIC SUBSTANCES AFFECTING AN ALTERATION IN IMMUNE FUNCTION *IN VIVO* AND *IN VITRO*

COMPOUND	CITATION	EFFECT
2,3,7,8–TCDD	Sonawane et al. 1988	
	Jennings et al. 1988	
	d'Argy at al. 1989	
	McConkey and Orrenius 1989	
	Gorski et al. 1988	Increased corticosterone at 25 µg/kg in S–D rats, decreased thymus weight, morphological changes in thymus & adrenal over starvation stress.
	Davis and Safe 1988	25 mg/kg A1254 with 3.7 nmol/kg TCDD (immunotoxic dose) reduced TCDD toxicity.
	Davis and Safe 1989	A1260, 1254, 1248, 1242, 1016, & 1232 ED50 to inhibit SRBC is 104, 118, 190, 391, 408, & 464 mg/kg or 0.28, 0.35, 0.66, 1.5, 1.5 & 2.0 nmol/kg, respectively. Reconstituted breast milk congeners required 50 mg/kg to antagonize 3.7 nmol TCDD.
	Fine et al. 1988	Maternal single dose 10 µg/kg led to TdT 70–90 percent inhibition in 4–11 day–old mice bone marrow. Thymic [TCDD] 1–31 fg/mg tissue.
	Luster et al. 1988.	2 µg/kg elicits T–dependent and T–independent antibody response *in vivo* and ED50 7 nM after *in vitro* additions to spleen culture.
2,3,7,8–TCDD	Spitzbergen et al. 1988	1 µg/kg caused decrease in lymphoid cells in thymus, splenic lymphoid depletion, hypocellularity of blood forming tissues in rainbow trout.
Aldicarb	Selvan et al. 1989	Suppresses macrophage–mediated cytotoxicity of tumor cells at 0.1 ppb i.p (f) C3H mice.

TABLE 13 (Cont.)

COMPOUND	CITATION	EFFECT
Mirex	WHO 1984	
PCB (See Table 15)	USPHS-ATSDR 1988	
	Shigematsu et al. 1978	
	Smialowicz et al. 1989	10 & 25 mg/kg after 15 week male Fischer 344 rats, thymic involution & NK cell activity and LP response only at 25 mg/kg.
	Smialowicz et al. 1989	Hepatomegaly at 1 mg/kg and thymic invol at 10 mg/kg after 5 weeks.
PCP	Bozelka and Salvaggio 1985	
TBT	WHO 1980	
	Snoeji 1987	
	Snoeji 1988	Dose causing 50 percent reduction in thymus weight was 18 mg DBTC & 29 mg TBTC/kg bw rats.
TBT	Smialowicz et al. 1989	2.5 mg/kg x 10 produced thymic invol. & mitogen response suppressed at 5 mg/kg, adult male Fischer rats. Or 5 mg/kg 3x/wk produced thymic invol in adults and preweanlings.
	Smialowicz et al. 1989	produced thymic invol in adults and preweanlings. NK suppressed in pups only at 10 mg/kg.
	Van Loveren et al. 1990	20 to 80 mg/kg TBTO in food to rats /6wks, dose response NK activity suppressed in lung tissue.
Toxaphene	Bozelka and Salvaggio 1985	MLR suppressed in adults at 20 mg/kg and at 10 mg/kg in pups.

Adapted from Bozelka and Salvaggio 1985
* = prenatal exposure

TABLE 13 (Cont.)

COMPOUND	CITATION	EFFECT
	Renana and Rao 1992	
HCB	Barnett et al. 1985*	Immunosuppressive in prenatal mice.
	Van Loveren et al. 1990	150 mg/kg to 450 in food 6 weeks suppressed NK activity dose response in rat lungs.
Lead	Bozelka and Salvaggio 1985	
	Buchmuller-Rouiller et al. 1989	
	Malviya et al. 1989	1 gm/d for 7d PbNO3 increased susceptibility to Ascaridia gallia.
Lindane (b-HCH)	Cornacoff et al. 1988	
	WHO 1976	
	Contrino et al. 1988	
	Reardon and Lucas 1987	
	Blakley 1990	
	van Velsen et al. 1986	Thymus weight loss
Mercury	Mirtcheva et al. 1989	0.5 mg HgCl2/kg bw s.c.3x/wk. Autoimmune response in female rats.
	Rossert et al. 1988	100 µg HgCl2/100 g bw s.c.3x/wk. Autoimmune response in male and female rats.
	Stiller-Winkler et al. 1988	3 µg Hg2 s.c. in murine hind foot pad stimulated T-cell-dependent enlargement of the popliteal lymph node (PLN).
	Reardon and Lucas 1987	Induces cytotoxic T-cells and interferon production in mice.
	USPHS. ATSDR 1988	Induces glomerulonephritis in rats.

TABLE 14

IMMUNOSUPPRESSIVE EFFECTS OF POLYCHLORINATED BIPHENYLS

COMPOUND	SPECIES	EFFECTS	REFERENCE
PCBs	Monkey	Increased natural killer cell activity, interferon levels, and thymosin alpha–1 levels	Tryphonas et al. 1991a
PCBs	Monkey	Decreased IgM and IgG response	Tryphonas et al. 1991b
PCBs	Monkey	Reduced antibody levels	Tryphonas et al. 1989
PCBs	Mouse	Inhibited splenic plaque–forming cell response	Howie et al. 1990
PCBs	Rat	Reduced activity of natural killer cells, reduced thymus weight	Smialowicz et al. 1989
PCBs	Monkey	Lowered antibody response	Colborn 1989
PCBs	Guinea pig	Reduced leukocytes and lymphocytes, induced thymic atrophy	Colborn 1989
PCBs	Rat	Suppressed T–cell response	Kerkvliet & Baecher–Steppan 1988
PCBs	Chick	Inhibits lymphoid development in the bursa of Fabricus	Nikolaidis et al. 1988
PCBs	Quail	Immunosuppressive response	Dieter 1974
PCBs	Guinea pig	Immunosuppressive response	Vos & De Roy 1972
PCBs	Mallard duck	Immunosuppressive response	Friend & Trainer 1970

The mechanism of thymic involution in mammals is poorly understood. In mice, TCDD severely impairs fetal liver and neonatal bone marrow prothymocyte activity, thereby disrupting the seeding of the thymus with prothymocytes (Fine et al. 1989, 1990a, b). TCDD administered to pregnant mice inhibits thymocyte maturation in embryos *in utero* (Blaylock et al. 1992) and decreases the number of thymic glucocorticoid receptors in both male and female rats in later life (Csaba et al. 1991).

The effects of TCDD on mature immune cells are diverse. Although TCDD increases natural killer cell (a type of T-cell) activity in the blood and spleen of mice, it decreases the proliferative response of spleen lymphocytes (Funseth and Ilback 1992). TCDD acts by impairing the function of helper T-cells, leading to an impairment of B-cell activation (Neubert et al. 1990; Tomar and Kerkvliet 1991; Lundberg et al. 1991), and suppression of B lymphocyte maturation and antibody synthesis (Clark et al. 1991). This is accomplished by alterations in tyrosine kinase activity that occurs within minutes of TCDD treatment (Clark et al. 1991). However, House et al. (1990) noted a dose-dependent decrease in activity in both T-dependent and T-independent antibody (IgM and IgG) forming cells.

In general, TCDD-induced immunosuppression requires induction of cytochrome P4501A1 (Gasiewicz and Rucci 1991). However, certain aspects of immunosuppression may operate through different mechanisms. Both T-helper cell and cytotoxic T lymphocyte activity disruption may be independent of TCDD binding to the Ah receptor (Kerkvliet et al. 1990a, b).

Mercury exposure can impair immune system function by altering the activity and levels of immune cells. Exposure via the placenta and milk impairs natural killer cell function in rats (Ilback et al. 1991). Immunosuppressive effects, including a 22 percent decrease in thymic weight and 50 percent reduction in thymic cells, occurred following 12 weeks of 3.9 μg/g oral dosing in mice (Ilback 1991). Mouse splenic T lymphocytes were activated to display cytotoxicity and produce interferon at 10μ of Hg^{++} (Reardon and Lucas 1987).

Mercury induces a significant autoimmune disease effecting the kidneys. Mercury exposure leads to production of antibodies to renal basement membranes, resulting in glomerulopathy (Bellon et al. 1982; Bernaudin et al. 1981; Andres 1984; Knoflach et al. 1986; Fukatsu et al. 1987; Guery et al. 1990; Pelletier et al. 1990; Pusey et al. 1990; Hultman and Enestrom 1992). Mercuric mercury, but not methylmercury, induces synthesis of metallothionein by the kidney cells only (Amdur et al. 1991).

2.2.5.4 Metabolic Impairment

Metabolic changes as the result of exposure to chemical contaminants have been documented in the mixed function oxidase (MFO) enzyme system of invertebrates, fishes, birds, and mammals (Table 15). Functionally, this system acts to metabolize steroid hormones and

xenobiotics for excretion. MFO enzymes such as aryl hydrocarbon hydroxylase (AHH) and ethoxyresorufin–O–deethylase (EROD) are found in the liver, kidney, intestines, and most body tissues. They respond to the presence of chemicals such as PCBs, PAHs, dioxins, and organochlorine pesticides. Although the elevation of MFO enzymes is not necessarily an indication of toxicity, it is an indicator of the presence of these particular substances and can be used as a measure or biomarker of toxic exposure (Rattner et al. 1989). The biological responses to AHH and EROD activity have been associated linearly with a number of toxic responses including body weight loss ("wasting") and thymic atrophy in rats, cleft palate in mice, and mild to severe porphyria, depending upon the species of animal exposed (Mason et al. 1985; Mason et al. 1986; Mason et al. 1987). In some instances, the metabolic product of the enzyme activity is more toxic than the original compound. Field investigators have used MFOs as measures of xenobiotic exposure and in several instances have shown an association between elevated enzyme activity and an adverse effect (Table 16).

Fish and Wildlife Studies

It has been suggested that MFO activity in a species is inversely related to the accumulation of an enzyme inducing xenobiotic in a species, i.e., MFO activity level may contribute to the amount of xenobiotic accumulated. Fish and fish–eating birds exhibit the lowest MFO activity; other birds are intermediate; and mammals have the highest activity (Rattner et al. 1989).

Fish

The National Benthic Surveillance Project (Varanasi 1989) reported metabolic disorders in fish from contaminated areas. A suite of metabolic bioindicators of contaminant exposure was field tested in three species of Puget Sound fish: English sole (*Parophrys vetulus*); starry flounder (*Platichthys stellatus*); and rock sole (*Lepidopsetta bilineata*), from five sites over a contamination gradient. Comparisons of the concentrations of 24 aromatic hydrocarbons and PCBs in sediment, fish liver PCB concentration, and fish bile fluorescent aromatic compounds (FACs) (a bioindicator of contamination and metabolite accumulation in fish bile) were made on seasonally–controlled samples. Although the results showed variation in response between tests, all were sensitive enough to differentiate the levels of contamination. The National Oceanographic and Atmospheric Administration (NOAA) also demonstrated a statistical link between aromatic contaminants and other metabolic effects such as induction of the MFO cytochrome P450 enzyme system in field and laboratory studies of the following fish: Atlantic croaker, black croaker, California halibut (*Paralichthys californicus*), Chinook salmon (*Oncorhynchus tshawytscha*), Coho salmon (*Onchorhynchus kisutch*), Dolly Varden (*Salvelinus malma*), English sole, flathead sole, hardhead catfish, hornyhead turbot, Pacific halibut (*Hippoglossus sp.*), rock sole, starry flounder, white croaker (*Genyonemus lineatus*) and winter flounder (*Pseudopleuronectes americanus*) (NOAA 1991).

MFO activity in lake trout (*Salvelinus namaycush*) and white suckers (*Catastomus commersoni*) from Lakes Ontario and Michigan was higher when compared with activity in fish

from Lakes Superior, Erie, and Huron (Hodson et al. 1989). MFO activity in Lake Michigan lake trout embryos as a result of parental exposure was 3.5 to 6.5 times higher than in embryos from hatchery stock. MFO activity abated in the embryos after several months in clean water (Binder and Lech 1984).

Wildlife

"Wasting" and egg shell thinning in colonial nesting birds were described among the earliest reports of wildlife damage in the Great Lakes (Gilbertson 1975). Ellenton and coworkers (1985) were the first to use enzyme induction as a measure of exposure as well as toxicity in field research (Table 17). Exposure to organic contaminants has been associated with MFO activity in birds and reptiles as well as fish.

Custer and Peterson (1991) studied black-crowned night-heron *(Nycticorax)* MFO activity to determine its applicability for use as indicators of U.S. estuarine contamination. Enzyme activity and pollutant load in black-crowned night-heron chicks in Chincoteague National Wildlife Refuge were compared with chicks from more polluted sites in Green Bay, Wisconsin and San Francisco Bay, California. In comparison to the Chincoteague reference site, San Francisco Bay chicks displayed significantly greater AHH activity.

Porphyria, a condition wherein heme biosynthesis is altered, results in the accumulation in the liver of porphyrins, precursors to hemoglobin. HCB, PCBs, and dioxins induce the accumulation of highly carboxylated porphyrins (HCPs) and are measurable in liver tissue and the blood. Their presence is used specifically as an indicator of exposure to PCBs, HCB, and TCDD (Marks 1985). The porphyrins are toxic and are components of the suite of lesions for diagnostic chick edema disease (Gilbertson 1992). The levels serve as distinct measures of change in the presence of the above organochlorine chemicals. The Canadian Wildlife Service has plotted the variation in highly carboxylated porphyrins in herring gulls from various locations around the Great Lakes (See Figure 5).

HCB caused porphyria cutanea tarda (PCT) in children, one year of age or less, whose mothers consumed HCB-treated wheat in an incident in Turkey during a famine (Jones and Chelsky 1986). All children exposed *in utero* expired within two years after birth.

The U.S. National Human Adipose Tissue Survey (Murphy et al. 1983) and a nationwide breast milk study in Canada (Davies and Mes 1987) found HCB 100 percent of the time in fat and breast milk, respectively. A recent report indicates that HCB over the ten year period between 1975 and 1985 remained constant or possibly increased in human adipose tissue (OWRS 1986). Regular fish eaters hold higher concentrations of HCB than lacto-vegetarians and mixed dieters (Noren 1983).

TABLE 15

ENZYME TEQ IN GREAT LAKES ANIMALS

Dioxin enzyme induction toxicity screening (TCDD equivalents) and specific dioxin and PCB congeners for which dose–response associations have been made with morbidity and mortality in wildlife populations.

Biologic Marker	Wildlife Species	Mortality and Morbidity Endpoints	Citations
TCDD equivalents 3,4,5,3',4'–penta PCB 3,4,3',4'–tetra PCB 2,3,7,8–TCDD	Forster's tern	embryonic mortality deformities	Kubiak et al. 1989
TCDD equivalents	Caspian tern	embryonic mortality deformities	Ludwig and Giesey 1990 Giesey et al. 1991
TCDD equivalents 3,4,5,3',4'–penta PCB 3,4,3',4'–tetra PCB 2,3,7,8–TCDD	DC Cormorant	embryonic mortality deformities egg mortality	Ludwig and Giesey 1990 Giesey et al. 1990 Tillit et al. 1992
TCDD equivalents 3,4,3',4'–tetra PCB	Lake trout	hatchability	Mac and Edsall 1989
TCDD equivalents	Coho salmon	embryonic mortality	Ludwig and Giesey 1990
TCDD equivalents	Herring gull	embryonic mortality deformities	Ludwig and Giesey 1990

TABLE 16

REVIEW OF MECHANISM OF ACTION OF COMPOUNDS OF CONCERN

	ACTIVITY AND CITATION		
COMPOUND	ENZYME INDUCERS	INHIBITORS OF GAP JUNCTIONAL COMMUNICATION	DISRUPTION OF ENDOCRINE CONTROL
2,3,7,8-TCDD	Silbergeld and Mattison 1987		Umbreit and Gallo 1988, Silbergeld and Mattison 1987, Gallo 1988, Romkes and Safe 1898
B[a]P	Bradlaw and Casterline 1979		
Chlordane	Traber et al. 1988 (intest.), Haake et al. 1987		Cranmer et al. 1984, Welsh et al. 1971
DDE	Bulger and Kupfer 1983, Haake et al. 1987	Zhong-Xiang et al. 1986, Warngard et al. 1988, Trosko and Chang (in press), Klaunig and Ruch 1987a, b, Ruch et al. 1987 (DDT)	Fry et al. 1987, Rattner et al. 1984, Bulger and Kupfer 1983, Fry and Toone 1981, Lundberg 1973
Dieldrin	Haake et al. 1987	Zhong-Xiang et al. 1986	Haake et al. 1987
HCB	Gutkina and Mishin 1986, Stewart and Smith 1986, Haake et al. 1987		Haake et al. 1987, Elissalde and Clark 1979
Lead			Rodamilans et al. 1988, USPHS. ATSDR 1988

TABLE 16 (Cont.)

ACTIVITY AND CITATION			
COMPOUND	ENZYME INDUCERS	INHIBITORS OF GAP JUNCTIONAL COMMUNICATION	DISRUPTION OF ENDOCRINE CONTROL
Lindane [g-HCH]		Zielmaker and Yamasaki 1986, Ruch et al. 1987 (g-HCH), Trosko and Chang (in press)	Uphouse 1987, Van Velsen et al. 1986, Van Giersbergen et al. 1984
Lindane [b-HCH]	Schroter et al. 1987, Van Velsen et al. 1986		Van Velsen et al. 1986, Van Giersbergen et al. 1985
Mercury			Veltman and Maines 1986, USPHS-ATSDR 1988, p. 57
Mirex	WHO 1984	Carlson et al. 1985, Rosenbaum and Charles 1986, Trosko and Chang in press	
PCBs	Safe 1984, Mason et al. 1986, 1987, 1988, Traber et al. 1988 (intest.)	Tsushimoto et al. 1983, Ruch et al. 1987 (Aroclor 1254), Trosko and Chang (in press)	Dieringer et al. 1979, Biessmann 1982
Toxaphene	Haake et al. 1987, WHO (Camphechlor) 1984, Chu et al. 1988	Trosko and Chang (in press)	Mohammed et al. 1985, WHO (Camphechlor) 1984

Laboratory And Mechanistic Studies

This section will deal with certain effects on systemic, cellular, and biochemical metabolism. Xenobiotics have an enormous effect on the body by their induction of metabolic enzyme systems. These enzymes regulate the metabolism of many endogenous chemicals, such as hormones, and foreign contaminants as well.

Systemic metabolic depression leading to slow starvation and eventual death is referred to as the wasting syndrome. The mechanistic basis of the wasting syndrome has proven to be particularly elusive. There are several different mechanisms by which the anorexia (loss of appetite) and hypophagia (decrease in food intake) of the wasting syndrome may occur. These include enzymatic induction of the mixed-function oxidase (MFO) system, neurological changes, and disruption of several different endocrine hormones, receptors, and feedback mechanisms. It is likely that the wasting syndrome is a manifestation of multiple biological effects. Refer to Table 17 for a summary of the different mechanisms implicated in the wasting syndrome.

The body has natural defenses to eliminate foreign compounds from its system. Many substances that are water soluble are rapidly eliminated by the kidneys and tend not to bioaccumulate. Alternately, organic compounds are less water-soluble, and are far more difficult to excrete. Organic xenobiotics are therefore oxidized to form water-soluble metabolites that can be further conjugated and excreted in the urine or bile (Lech et al. 1982; Payne et al. 1987). The major means of xenobiotic oxidation are accomplished through a complex metabolic pathway referred to as the mixed-function oxidase system.

The mixed-function oxidase system, or MFO, is located in the microsomal portions of various tissues, especially of the liver. It is characterized as comprising an electron transport system with cytochrome P450, requiring NADPH (or NADH) as a cofactor, and being capable of oxidizing many different kinds of substrates (i.e., substrate nonspecificity). Cytochrome P450 is the component of the MFO system that actually binds to both oxygen and substrate molecules. Other enzymes, such as NADPH-cytochrome-c-reductase (a flavoprotein) mediate the transport of electrons from NADPH to cytochrome P450.

Cytochrome P450 consists of a family of hemoproteins called monooxygenases. The entire system of monooxygenases collectively forms the MFO system. In humans there are over 30 different cytochrome P450s identified (Guengerich 1992). Many monooxygenases are capable of oxidizing different substrates (Guengerich 1991). This enables the cytochrome system to oxidize many different natural substances, as well as xenobiotics. Natural substrates in the body include steroid hormones, prostaglandins, fatty acids, leukotrienes, biogenic amines, pheromones and plant metabolites (Nebert and Gonzalez 1987).

The MFO system is the bodies first line of defense against xenobiotics (Payne et al. 1987), including many drugs, chemical carcinogens, mutagens, and environmental contaminants (Nebert and Gonzalez 1987). The induction of monooxygenases is relatively non-specific. A single xenobiotic can induce the production of many members of the cytochrome system. For

example, seven different Cytochrome P450s may be induced by barbiturates (Guengerich 1992). This makes the MFO system capable of responding to a wide variety of xenobiotics. Further, once the MFO system is induced by one xenobiotic, it is capable of rapidly responding to others. This also makes MFO induction one of the most sensitive physiological indicators of environmental pollution (Payne et al. 1987; Narbonne 1991; van der Oost et al. 1991; Pesonen et al. 1992). MFO systems are wide-spread among species, although there is considerable variability in specific enzymes (Nebert et al. 1981).

The mechanism of MFO induction is best understood for dioxins (Figure 6). For TCDD to produce an effect, it must bind to the aromatic hydrocarbon (Ah) receptor, forming the inducer-receptor complex that is transported to the nucleus by the Ah receptor nuclear translocator protein (arnt) (Reyes et al. 1992). The inducer-receptor complex subsequently interacts with one or more of the Ah-responsive elements (AhREs) located upstream from the transcriptional initiation site (Carrier et al. 1992). Transcription of a gene such as CYP1A1 (cytochrome P4501A1) requires phosphorylation by protein kinase C in order to form a transcriptional complex (Carrier et al. 1992).

CYP1A1 and its associated enzyme product, the aryl hydrocarbon hydroxylase (AHH) assist in detoxification of polycyclic aromatic hydrocarbons (Safe 1986; Landers and Bunce 1991). The CYP1A1 gene exhibits differences in induction response between males and females (Jones et al. 1991). Microsomal enzyme activity may be markedly increased in females, but limited in males. Vitamin C (ascorbic acid) reduces the microsomal aryl hydrocarbon hydroxylase (AHH) activity induced by TCDD in mice (Kiyohara et al. 1991). Alternately, PCBs increase cellular levels of ascorbic acid (Nagaoka et al. 1991).

PCBs induce, in hepatic microsomes *in vivo*, a variety of different forms of the cytochrome P450 enzyme systems involved in the metabolism of xenobiotics (Borlakoglu et al. 1990). This includes increases in cellular levels of AHH (Nagaoka et al. 1991). PCBs covalently bind to DNA following metabolic activation, although the more highly chlorinated congeners are poorly metabolized *in vivo* and do not readily form covalent adducts (Safe 1989). A linear association exists between PCB dose and cytosolic protein binding; between protein binding and enzyme induction; and between enzyme induction, immune suppression, teratogenicity, and wasting (Safe 1984; Safe et al. 1985; Mason et al. 1986; Mason et al. 1987).

TABLE 17
MIXED FUNCTION OXYGENASE RESPONSES DOCUMENTED IN FREE-RANGING WILDLIFE

Species	Age	Sex	Site	Comparison or Control	Tissue Residue or Potential Exposure	MFO Type	Response Change	Reference
Herring gull	20- and 25-day old embryo	--	Great Lakes	Association between MFOs and residues; unpolluted control site	Pentachlorobenzene TCDD	AHH	+	Ellenton et al. 1985
Herring gull	25-day embryo	--	Great Lakes	Association between MFOs and residues; unpolluted control site	DDE, Mirex, Hexachlorobenzene, PCBs	EROD APDM AmH	+ - -	Boersma et al. 1986
Forster's tern	1-day-old hatchling	--	Great Lakes	Unpolluted control site	PCBs, TCDDs, Polychlorinated dibenzo-p-dioxins	AHH	+	Hoffman et al. 1987
Herring gull	21 and 25 day embryo 2, 7, 1, and 21 day-old nestling	-- Male and Female	Newfoundland	Association between MFOs and residues	DDE, Dieldrin, Heptachlor epoxide, Oxychlordane, Hexachlorobenzene and PCBs	AHH APDM EROD Cytochrome P-450	0 0 0 +	Peakall et al. 1986
Black-crowned night-heron	Pipping embryo	--	San Francisco Bay	Association between MFO's and residues; captive control	Organochlorines, PCBs	AHH	0	Hoffman et al. 1986
American robin	Adult	--	Pine plantations in Wisconsin	Unpolluted control site	TCDD, Polychlorinated dibenzo-p-dioxins	AHH EROD	+ +	Martin et al. 1987

TABLE 17 (Cont.)

Species	Age	Sex	Site	Comparison or Control	Tissue Residue or Potential Exposure	MFO Response		Reference
						Type	Change	
Double-crested cormorant			Great Lakes	Across a geographic pollution gradient	PCBs		+	Tillet et al. 1992
Razorbill and puffin	Adult	Male and Female	Saltee Islands, Ireland Isle of May and Outer Hebrides, Scotland	Association between MFOs and residues	PCBs	Aldrin epoxidase Hyrdoxylation of dieldrin analogue	0 0	Knight and Walker 1982
Pigeon	--	--	Lucknow, India	Reared in captivity	DDE, DDT, Hexachlorocyclohexane, Lindane	AHH	+	Kaphalia et al. 1981, Husain et al. 1981
Black-necked grebe	Adult	--	Marano, Italy	Various intervals of residence at polluted site	DDE, Hexachlorobenzene, PCBs	Aldrin epoxidase EROD	+ +	Fossi et al. 1986
Black-headed gull	--	--	Central Italy	Association between MFOs and residues; dump versus lagoon	PCBs	Aldrin epoxidase EROD	+ +	Fossi et al. 1986
Cotton rat	Adult	Male	Texas	Unpolluted control site	Arsenical herbicides, Dieldrin, Petroleum hydrocarbons, PCBs	AnH Cytochrome P-450	0 —	Rattner et al. 1986, Rattner et al. 1987

Mercury is a potent, nonspecific enzyme poison. It produces its effects by releasing mercuric ions, which readily form covalent bonds with sulfhydryl groups (Winek et al. 1981). This results in the inhibition of metabolic enzymes, denaturation of proteins, and disruption of cell membranes (Bryson 1989; Chetty et al. 1990; Gill 1990; Boadi et al. 1991; Dieter et al. 1992; Wigfield and Eatock 1992; Anner and Moosmayer 1992; Suresh et al. 1992). However, methylmercury does induce AHH activities (Boadi et al. 1991, 1992).

Metabolism of xenobiotics is normally thought of a "detoxification," but this is not always the case. Sometimes, in the body's attempt to rid itself of foreign materials, it actually creates reactive intermediates that are more toxic than the original compound (Anders 1985; Thakker et al. 1985; Nebert and Gonzalez 1987; Butler et al. 1989; Aoyama et al. 1990; Guengerich 1992). This type of transformation is referred to as "activation". P450 cytochromes are involved in the metabolic activation of polycyclic aromatic carcinogens (Fujii-Kuriyama et al. 1990).

Further, by inducing the MFO system, xenobiotics stimulate changes in enzymes regulating other body functions. Associated with the wasting syndrome are changes in carbohydrate homeostasis. Correlated with the reduction in feeding is a decrease in formation of the essential blood sugar glucose (gluconeogenesis) by the livers of rats exposed to TCDD. Both appetite lose and reduction of hepatic enzyme activity occurred in the same dose ranges, suggesting a possible cause and effect relationship (Weber et al. 1987, 1991). In birds, TCDD-induced wasting is associated with impaired carbohydrate production (Lentnek et al. 1991). In human cells, TCDD completely inhibited the conversion of glucose to lactate (Narasimhan et al. 1991).

Changes in regulatory enzymes of the MFO system affect other systems as well. Particularly important are changes in sex steroid levels that influence reproductive cycles, behavior, and fertility. These effects of xenobiotics on behavior and reproduction will be discussed under the appropriate section.

FIGURE 5

PORPHYRIN LEVELS IN LIVERS OF GREAT LAKES HERRING GULLS IN 1985

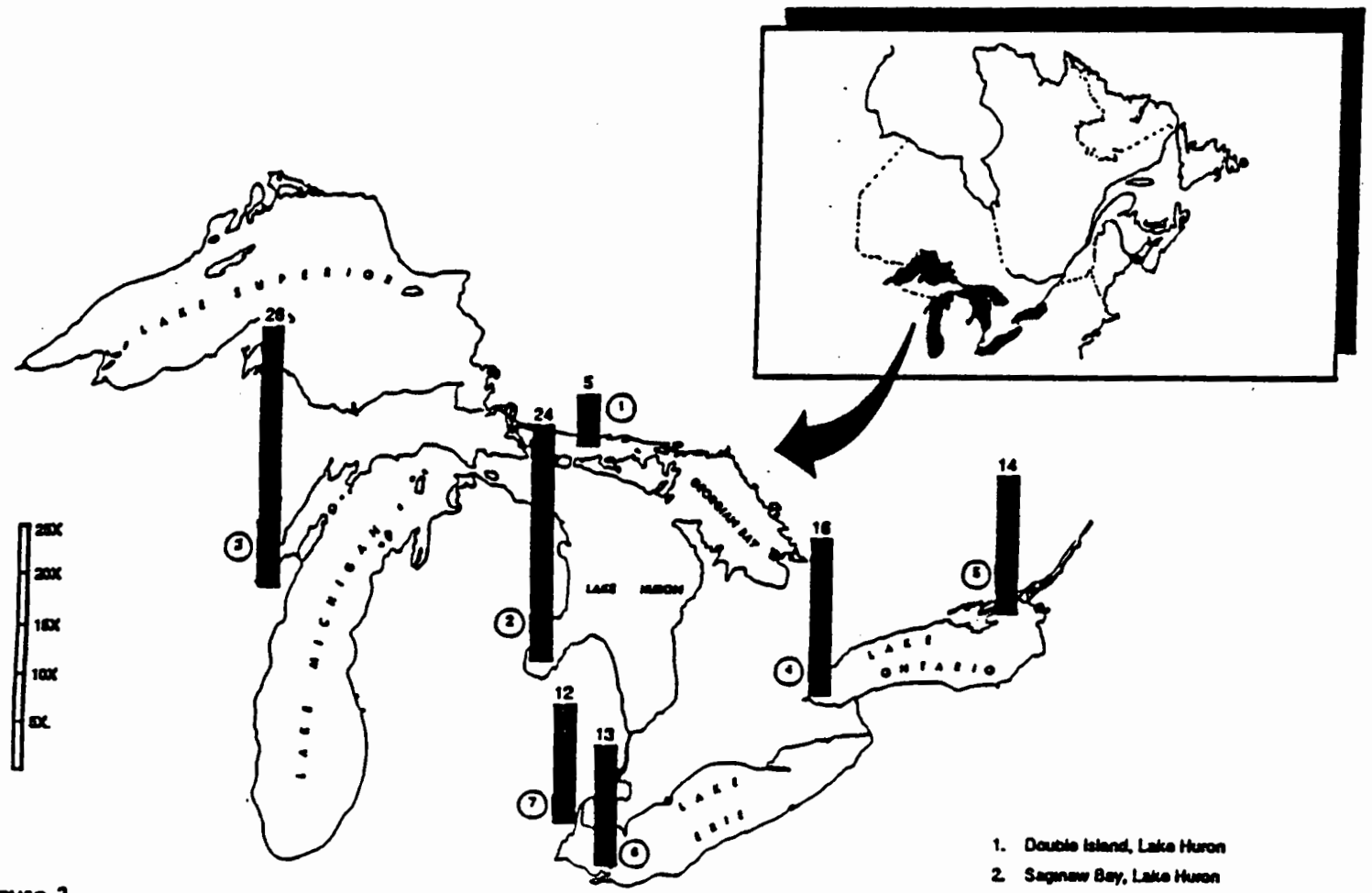


Figure 3

Porphyrin levels in livers of Great Lakes herring gulls in 1985. Median levels of highly carboxylated porphyrin levels in livers collected from seven Great Lake colonies are expressed as multiples of the median levels in herring gulls from the atlantic coast. Location of Great Lakes sites are identified with circled numbers.

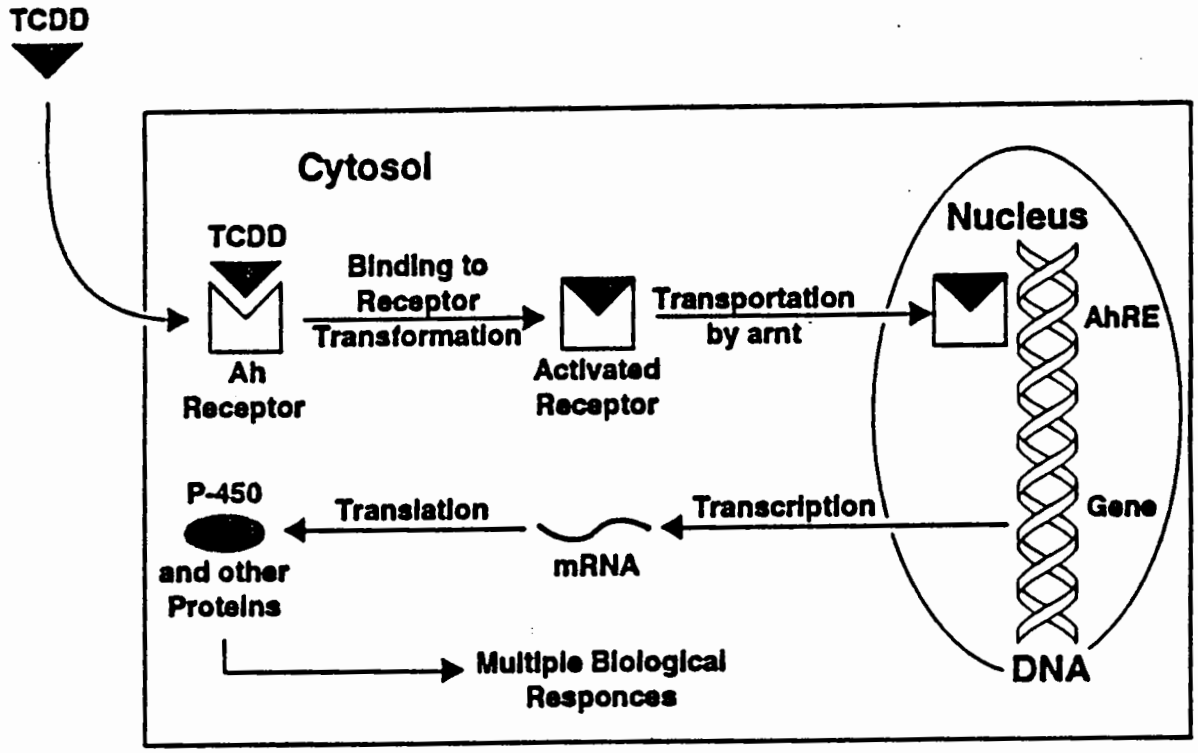
Source: G. Fox (Canadian Wildlife Service).

1. Double Island, Lake Huron
2. Saginaw Bay, Lake Huron
3. Green Bay, Lake Michigan
4. Hamilton Harbour, Lake Ontario
5. Snake Island, Lake Ontario
6. Middle Island, Lake Erie
7. Detroit River

Atlantic Coast Sites are Shown in Map Inset

FIGURE 6

MECHANISM OF DIOXIN-Ah RECEPTOR ACTION



Source: Modified from Landers and Bunce, 1991

Proposed mechanism of dioxin action through the Ah-receptor. TCDD enters the cell where it is bound by the Ah-receptor (aromatic hydrocarbon) molecule. The TCDD and its bound receptor are transformed into an activated complex, which is transported into the nucleus by arnt (Ah-receptor nuclear translocator protein). The activated complex binds to the AhRE (Ah-responsive elements), enhancing transcription of structural genes into mRNA (messenger RNA). The mRNA is translated into several cytochrome P-450 enzymes and other proteins, resulting in an array of biological responses.

TABLE 18

MECHANISMS IMPLICATED IN THE WASTING SYNDROME

Target Organ	Mechanism	Process Affected
Liver	Mixed-function Oxidase System	Carbohydrate Metabolism
Brain	Neurotransmitters	Feeding Behavior
Thyroid	Thyroxine & Triiodothyronine	Cellular Metabolism Brown Fat Metabolism
Adrenal Gland	Corticosterone	Gluconeogensis
Pancreas	Insulin & Glucagon	Blood Glucose Levels

2.2.5.5 Nervous System and Behavioral Impairment

Wildlife Studies

Overt and subtle behavioral changes have been identified in wildlife and human populations who consumed contaminated fish. Wildlife populations exhibited changes in sexual and nesting behavior (Burger 1990; Conover 1984; Conover and Hunt 1984a, 1984b; Kovacs and Ryder 1981; Kubiak et al. 1989; Fox and Weseloh 1987; Fry et al. 1989; Fry and Toone 1981; Nisbet and Drury 1984; Shugart et al. 1988). Diamond (1989) points out that these changes in sexual behavior were not reported before 1950 in aquatic birds. The onset of these changes coincides with the first reports on eggshell thinning and gross mortality in wildlife populations around the Great Lakes (Colborn 1988) and supports the hypothesis that post World War II chemical production has an influence on ecosystem health (Colborn 1991) (Figure 7).

Populations of Great Lakes herring gulls, Forster's terns, and ring-billed gulls suffering reduced reproductive success also exhibited behavioral changes such as female-female pairings, aberrant incubation activities, and nest abandonment (Shugart et al. 1988; Fox and Weseloh 1987). Female-female pairings of herring gulls resulted in supernormal clutches, 4-8 eggs per nest rather than 3 eggs (Fox and Weseloh 1987; Peakall and Fox 1987). Although egg-laying capacity was not impaired, only 10 to 30 percent of the eggs were fertile (Shugart et al. 1988).

Nest abandonment was observed and hatching success was reduced in Green Bay (26 percent) versus inland (88 percent) Forster's tern colonies (Hoffman et al. 1987; Kubiak et al. 1989). Fox et al. (1978) found a positive correlation between abandonment (time unattended) of Lake Ontario herring gull nests and the level of contaminants in the eggs. Follow-up egg-swapping field studies for both the herring gull and Forster's tern determined that extrinsic parental behavior contributed to the intrinsic factors also affecting reproduction (Peakall et al. 1980; Kubiak et al. 1989). For a description of the Forster's tern study see Section 2.2.5.3. In a herring gull study on Lake Ontario in the early 1970s, Peakall and coworkers (1980) found that contamination levels of the colonies determined hatchability.

Supernormal clutches were also observed in the ring-billed, California, and western gulls of Oregon and Washington (Conover 1984; Conover and Hunt 1984a, b). Increase in female-female pairing correlated with the reduction in numbers of male birds during the breeding season. A frequency of double-nests and/or supernormal clutches (0.0005-0.01 percent) in New England herring gulls was compared with Great Lakes and West Coast observations (0.3 percent) (Nisbet and Drury 1984).

The New England gulls held little or no detectable DDT. Hunt and coworkers (1980) reported an incidence of 14 percent in female-female pairing among western gulls on Santa Barbara Island, California. Using museum specimens, Conover and Hunt (1984a) sexed post-1950 and pre-1940 western gulls and found a significantly lower male to female ratio in the post-1950 birds. Fry and Toone (1981) demonstrated that feminization (abnormal growth of oviducts and ovarian tissue) of male embryos occurred with exposure of wild adults in the field to DDT. The reduction in breeding male birds leading to female-female pairing and supernormal clutches was hypothesized to be from increased male mortality or feminization of male birds from contaminant exposure (Conover and Hunt 1984b; Nisbet and Drury 1984; Fry and Toone 1981).

Other behavioral change from DDT metabolites and DDT analogs was demonstrated in experiments on the American kestrel (*Falco sparverius*) with *in ovo* exposure to p,p'-dicofol (registered name Kelthane), a structural analog of DDT and DDE (Fry et al. 1989). First and second generation studies resulted in the following: testicular feminization of first generation males from Kelthane, dicofol, and DDE exposure; and a dose-response reduction of male aggressive behavior and infertility from Kelthane.

Adult rats fed a 30 percent diet of salmon from the Salmon River, a tributary to Lake Ontario, developed an aversion to stress after 20 days (Daly 1989). All the rats fed Lake Ontario salmon were hyper-reactive to stressful events such as reductions in food rewards, mild shocks, and novel environments compared with rats fed Pacific salmon or no salmon. The same effects were seen after a 10 percent diet fed for 60 days (Daly 1991). In a later study, female rats were fed Lake Ontario, Pacific, or no salmon from the day they were placed with males until their rat pups were 7 days old. Their pups continued to nurse until 21 days old and were never fed Lake Ontario fish. Nonetheless, all pups from dams fed Lake Ontario fish exhibited hyper-reactivity to stressful events when tested as juveniles and as adults (Daly 1992b). Total PCBs and mirex

FIGURE 7

EFFECTS REPORTED IN GREAT LAKES WILDLIFE SINCE WORLD WAR II

Species	Population Decline	Reproductive Effect	Eggshell Thinning	Metabolic Changes "Wasting"	Deformities	Target Organ Damage	Behavioral Changes	Hormonal Changes	Immune Suppression	Generational Effects	Tumors
Bald Eagle	X	X	X	X	X		X			X	
Beluga Whale	X		N/A		X	X		X	X		X
Black-Crowned NH	X	X	X		X						
Caspian Tern	X	X		X	X		X			X	
Chinook/Coho Salmon	N/A	X	N/A			X		X		N/A	X
Common Tern	X	X		X		X	X		X		
D.C. Cormorant	X.	X	X	X	X	X	X			X	
Forster's Tern	X	X		X	X	X	X			X	
Herring Gull	X	X	X	X	X	X	X	X	X	X	
Lake Trout	X	X	N/A	X			X			X	
Mink	X	X	N/A	X		X				X	
Osprey	X	X	X								
Otter	X		N/A								
Ring-Billed Gull		X		X	X				X		
Snapping Turtle	X	X	X	X	X	X				X	

Observed effects that have been reported in the literature.

Effects reported in Great Lakes wildlife since World War II in populations dependent upon fish from the lakes.
Adapted from: Colborn (1991)

were the only contaminants quantified in the fish and the brains of the rats in the studies (Hertzler 1990). Both contaminants were significantly higher in the Lake Ontario fish and rats on the Lake Ontario fish diet compared with the Pacific Ocean fish- and mash-fed rats. In concurrent studies, researchers demonstrated an inverse association between tissue dopamine production and several non-dioxin-like PCB congeners (2,4,4'; 2,4,2',4'; 2,4,2',4',6') found in the fish Daly fed her rats (Seegal et al. 1985; Bush et al. 1990; Shain et al. 1990; Seegal 1992a, b).

The children of women who consumed Lake Michigan fish two to three times a month exhibited subtle changes in cognitive processing and altered activity levels (Jacobson et al. 1985; Rogan et al. 1988; Swain 1988; Jacobson et al. 1989; Winneke et al. 1989; Jacobson et al. 1990; Tilson et al. 1990; Jacobson et al. 1992). Children accidentally exposed *in utero* to cooking oil contaminated with PCBs and dibenzofurans exhibited similar neurological decrements (Rogan et al. 1988). Similar psychomotor events were documented in a North Carolina cohort of infants whose mother's milk delivered equivalent levels of PCB as those determined in the Lake Michigan mother's milk (Rogan et al. 1986). In each study neurological events were observed at the same level of PCB in breast milk. However, the neurological changes appeared not to persist in the North Carolina cohort as they did in the Lake Michigan cohort. Different instruments were used for testing in the two studies.

An association was found between the activity level in four-year old breast—fed children and concentrations of PCBs in the mothers milk (Jacobson et al. 1992). The children were exposed to elevated levels of PCBs as the result of their mothers' Lake Michigan fish consumption or their mothers' having consumed PCB-spiked farm products via contaminated silage. Hypotonicity and hyporeflexivity were increased in those children who nursed for more than a year and whose mothers' milk held the highest concentrations of PCB. Mothers' milk with PCB levels exceeding 1000 ppb contributed 0.19 ± 0.03 ppb per week to the offspring's serum at age 4. Mean serum concentration at 4 years was 5.1 ± 3.9 ng/ml in children who breast fed for 6 months, 1.2 ± 1.6 ng/ml for less than 6 months, and 0.3 ± 0.7 ng/ml for those who did not breast feed. In both cohorts, growth retardation as the result of *in utero* exposure persisted in a dose-dependent manner through age four and was observed, along with the neurotoxicological effects. Reduction in activity was also related to the youngsters' PCB body burden. The effects were more pronounced in females than males. Seventeen of the breast-fed children, all from mothers' with high PCB milk concentrations, refused psychological testing. This finding is consistent with the rat studies cited above (Daly 1992a).

Using the results of laboratory animal studies and the Jacobsons' studies, Tilson et al. (1990) determined that, neurotoxicolologically, humans are four orders of magnitude more sensitive to PCBs than rodents. In their analysis, they found that contemporary levels of PCBs transferred to human offspring *in utero* were associated with "...hypotonia, hyporeflexia at birth, delay in psychomotor development at 6 and 12 months, and poorer visual recognition memory at 7 months" (p. 239). The above effects are not visible and would ordinarily go undetected. In this case, skilled psychologists, unaware of the exposure history of the child, detected the effects in the children of women who ate Lake Michigan fish. These effects were found in the children of women who represented the upper 95 percent in a normal population based on PCB exposure.

Laboratory And Mechanistic Studies

There are many different types of behavioral impairment brought about by xenobiotic contaminants. Some affect reproductive behaviors, ranging from inappropriate courting and mating behaviors to miscare of eggs or young. Others involve the anorexia and hypophagia associated with the wasting syndrome. It is apparent that xenobiotic contaminants operate through a variety of neurologic mechanisms that ultimately lead to behavioral impairment.

The treatment of animals with xenobiotics brings about many of the behavioral abnormalities seen in wildlife from polluted areas. Feeding ring doves mixtures of DDE, PCB, and mirex produced behavioral abnormalities similar to those observed in Lake Ontario herring gulls (i.e., abnormal incubation behavior). These effects were dose-related to decreases in circulating androgens in males, estrogens and progesterone in females, and thyroxine in both sexes. Prolactin (which influences behavior in many vertebrates) was also altered in some individuals (McArthur et al. 1983).

Many behavioral effects are not due simply to changes in the endocrine system, but to direct effects of xenobiotics on the brain. In pigeons, 1 percent of PCBs administered was found in the brain within 120 hours of treatment (Borlakoglu et al. 1991). PCBs have been shown to accumulate in the brains of cod and trout (Ingebrightsen et al. 1990) and TCDD in the brain of cod (Ingebrightsen et al. 1991). Administration of TCDD directly to the intracerebroventricular fluid in rats produces significantly stronger reactions than peripheral administration, suggesting that the central nervous system plays an important role in TCDD toxicity (Pohjanvirta et al. 1989).

One of the most obvious effects of xenobiotics on wildlife is the wasting syndrome. TCDD treatment of rats leads to a decrease in food intake (hypophagia) and aversion to eating energy-providing foods. The neurological bases of altered satiety levels have been difficult to deduce. Studies have linked TCDD-induced wasting in rats with increased levels of serotonin (a neurotransmitter), or its precursor, tryptophan, in the brain (Rozman et al. 1991). However, TCDD can cause wasting even if serotonin levels are artificially reduced (Stahl et al. 1991), suggesting that factors other than serotonin are involved. Stahl and Rozman (1990) concluded that the effect of TCDD does not involve the brain, but rather a peripheral appetite suppressive (feedback) mechanism outside the central nervous system. Pohjanvirta and Tuomisto (1990a, b) suggest that hypersensitivity of the central nervous system to peripheral satiety signals coupled with hyporesponsiveness to metabolic energy deficit cues are involved in the wasting syndrome mechanism.

Dopaminergic neurons of the brain are particularly sensitive to environmental and pharmacological agents (Seegal et al. 1991a). The neurologic effect of PCBs and TCDD is correlated with decreased levels of the neurotransmitter dopamine (Russell et al. 1988; Seegal et al. 1991b). However, in rats exposed to 50 µg/kg TCDD, only slight changes in dopamine and several other aminergic neurotransmitters were noted from 4 to 76 hours following exposure. Although TCDD causes changes in brain aminergic neurotransmitter systems, the changes were

minor and it is unlikely that aminergic systems are solely responsible for TCDD-induced hypophagia (Tuomisto et al. 1990).

The degree of PCB chlorination determines if dopaminergic functions will be altered in the peripheral or central nervous systems (Seegal et al. 1988). Following exposure to Aroclor 1016, dopamine concentrations were significantly reduced in the brain of monkeys. Only three PCB congeners (2,4,4'; 2,4,2',4'; and 2,5,2',5') were subsequently found in the brain. These congeners were shown to reduce cellular dopamine concentrations in cells cultured *in vitro*, whereas planar, dioxin-like congeners (3,4,4',4', and 3,4,5,3',4') did not (Seegal et al. 1990). Studies in primates indicate that it is PCBs themselves, not their metabolites, that are responsible for neurotoxic effects (Shain et al. 1991). These studies, both *in vivo* and *in vitro*, suggest that PCBs may reduce dopamine concentrations through a novel mechanism and not through the Ah-receptor complex responsible for both immunotoxic and hepatotoxic changes following exposure to dioxin and dioxin-like PCBs (Seegal et al. 1990; Shain et al. 1991).

TCDD also may impair behavior and nervous system functions through disruption of endorphins and their receptors. Endorphins are natural brain peptides exhibiting morphine-like analgesic properties that may regulate behavior. TCDD causes perturbations in hypothalamic beta-endorphin concentrations and brain mu opioid receptor numbers, which may contribute to the mechanisms by which TCDD leads to decreased food intake and the wasting syndrome (Bestervilt et al. 1991).

DDT and its analogs appear to alter behavior through both endocrine and neurological mechanisms. The sexual (lordosis) behavior of adult female rats has been modified by single dose exposure to DDT. Although both o,p'-DDT and p,p'-DDT decreased lordosis behavior, they did so by different mechanisms. Whereas o,p'-DDT altered behavior by disrupting the estrous cycle due to its estrogenic properties, p,p'-DDT had a major effect on the female's proceptivity and receptivity without modifying her reproductive cycle (Uphouse and Williams 1989). Administration of p,p'-DDT decreased the level of the neurotransmitter serotonin within hours of treatment (Uphouse et al. 1990).

DDT has a tremendous influence on development of the nervous system in embryos. Neonatal exposure of mice to DDT caused changes in cholinergic receptors in the brain. Subsequently, these same mice exhibited learning disorders as adults (Eriksson et al. 1990b). A single oral dose of low-level DDT (1.4 mμmol/kg) to neonatal mice led to a permanent hyperactive condition as adults (Eriksson et al. 1990a).

In every animal species studied, the nervous system is adversely effected by methylmercury (WHO 1990). Further, methylmercury is one of the most potent neurotoxins known (Pryor et al. 1983), and is readily transported across the blood-brain barrier (Aschner and Aschner 1990; Kerper et al. 1992). Lesions are frequently observed in the granular layer of the cerebellum (Herigstad et al. 1972; Falk et al. 1974; Chang 1977; Davies et al. 1977; Jacobs et

al. 1977). In humans, the nervous system is the principal target of methylmercury exposure (Who 1990; Amdur et al. 1991), with the fetus of exposed mothers being particularly susceptible to deleterious effects (Cox et al. 1989). Damage to the brain is highly localized in the visual cortex, granular layer of the cerebellum, and sulci (WHO 1991).

Prenatal exposure of offspring to doses that do not effect the mother produce abnormal behavior in animals (Spyker et al. 1972; Bornhausen et al. 1980; Zimmer et al. 1980; Shimai and Satoh 1985; Elsner et al. 1988). In monkeys exposed from birth to seven years of age, overt behavioral effects were not manifested until they were 13 years old, demonstrating delayed effects of mercury long after exposure (Rice 1990). Effects include hydrocephalus, decreased cerebral cortex thickness, and increased hippocampus thickness (Kutscher et al. 1985).

Neurotransmitters and their receptors in the brain are effected by mercury exposure (Kobayashi et al. 1979, 1981; Concas et al. 1983; Atchison and Narahashi 1982; Quandt et al. 1982; Atchison 1986; Komulainen and Tuomisto 1987). Serotonin concentrations are increased in rats following a single dose of 5.0 mg mercury/kg delivered as methylmercury on postnatal day 2 (O'Kusky et al. 1988). Noradrenaline levels were increase significantly in the cerebellum of rats 50 days following parturition when exposed to low doses (3.9 mg/kg in diet of dam) during gestation and lactation (Lindstrom et al. 1991). The maturation of catecholamine neurotransmitter systems in rats are adversely effected by early postnatal exposure (Bartolome et al. 1982).

The mechanism of mercury action in the brain is complex. In developing brains, some effects are do to decreased motility of developing astrocytes (Choi and Lapham 1980), alterations of cell membrane surface charge (Peckham and Choi 1986; Bondy and McKee 1991), disruption of cell–cell recognition (Jacobs et al. 1986), and reduced myelination (Annau and Cuomo 1988). Cell division is blocked during metaphase (Sager et al. 1982, 1983; Rodier et al. 1984; Slotkin et al. 1985; Howard and Mottet 1986; Vogel et al. 1986) due to disruption of microtubules by methylmercury (Imura et al. 1980; Sager et al. 1983; Miura and Imura 1987). Methylmercury also disrupts levels of nerve growth factor in developing rat brains (Larkfors et al. 1991). Protein synthesis also is impaired (Cheung and Verity 1985; Sarafian and Verity 1985, 1986; Thomas and Syversen 1987). Male mice are more sensitive than females, which is consistent with observations in humans (Sager et al. 1984; Choi et al. 1978).

There are a wide variety of neuronal and behavioral effects caused by xenobiotic compounds (Table 19). These range from altering neurotransmitters and enzyme activities, disordering cell membranes, impairing ion channels through membranes, and disrupting cellular cytoskeletal elements. It is clear that we do not fully understand the mechanism of action of any xenobiotic on the nervous system. A single xenobiotic may have many different effects, which are brought about through multiple mechanisms.

TABLE 19

BEHAVIOR AND NEUROLOGIC EFFECTS OF XENOBIOTICS

COMPOUND	SPECIES	EFFECTS	REFERENCE
DDT	Cells	Disordered brain cell membranes	Antunes–Madeira & Madeira 1990
DDT	Rat	Decreases glycine levels in pons and medulla	Truong et al. 1988
DDT	Rat cells	Binds to sodium channels, causing persistent activation	Lombet et al. 1988
DDT	Porcine cells	Inhibits assembly of brain cell tubulin	Albertini et al. 1988
DDT, chlordecone	Rat cells	Inhibits ATPases involved in ion transport at nerve synapse	Kodavanti et al. 1988
DDT, PCBs, chlordane, lindane, toxaphene, heptachlor	Mouse cells	Stimulate protein kinase C	Moser & Smart 1989
Salmon contaminated with DDT, PCBs, DDE, mercury, dioxin	Rat	Increase behavioral reactions to negative feeding events	Daly 1991
2,3,7,8–TCDD	Rat	Improper hypothalmic imprinting in males	Peterson 1992

2.2.5.6 Endocrine Disruption

The endocrine system regulates physiological processes through a group of chemicals called hormones, which are released by the endocrine organs and are transported via the blood to other sites in the body where they exert their effect. They regulate responses to stress, coordinate regulation of metabolism among muscle, liver, and fat, and coordinate function over time, such as the changes required for normal sexual development and reproductive ability (Hedge et al. 1987). Laboratory and field studies with freshwater and marine animals provide evidence that xenobiotics are possibly contributing to the endocrine problems seen in the Great Lakes, and other aquatic and marine systems. Effects from endocrine disruption such as thyroid disorders, hormone deficiencies, secondary sex characteristic abnormalities, parental behavior change, and hermaphroditism are found in many aquatic populations where elevated concentrations of the chemicals of concern are found.

Wildlife Studies

No adult Great Lakes salmon (pink, coho, and chinook) have been found without an enlarged thyroid ("goiter") since 1974 by a team of researchers from Guelph University (Leatherland 1992). Iodine deficiency was ruled out as a causal agent because Great Lakes fish held comparable amounts of iodine to Northwest Pacific control fish. Thyroid enlargement and reduced plasma thyroxin (T4) levels were induced in a dose-response manner in rats fed diets of Great Lakes salmon, but were not inducible in fish fed the same diet (Leatherland 1992). No contaminant analyses accompanied these findings.

Thyroid enlargement was also observed in the Great Lakes herring gulls in significantly greater frequencies than in herring gulls from the Bay of Fundy (Moccia et al. 1986). Significant differences were reported among and within lakes for the occurrence of increased thyroid mass and thyroid tissue abnormalities, including epithelial cell hyperplasia, smaller follicular diameter, taller epithelial cells, and less cellular colloid. Again, iodine deficiency was ruled out as a causative agent. Exposure to environmental contaminants as a causative agent was supported by geographic distribution of the effects as well as laboratory studies associating PCBs, DDT, dieldrin, mirex, and heavy metals with the same thryoid anomalies (Moccia et al. 1986; Government of Canada 1991). Fox and Peakall (1991) provided further evidence by demonstrating an association between thyroid disorders and an environmental pollution gradient. They also found that severity of goiter in Lake Ontario decreased in subsequent collections, as the contaminant load decreased, liver PCB level was significantly correlated with degree of enlargement, and severity of thyroid enlargement was associated with retinoid depletion.

Other signals of endocrine disruption in salmon include premature sexual maturation while never reaching full maturity (with loss of reproductive function accompanied by reduction in expression of male hooked jaw and colored flanks), loss of sexual dimorphism (hermaphroditism in males and females), low plasma estradiol and dihydroxyprogesterone levels, and low fertility and embryo mortality resulting from low plasma steroid hormone levels (Moccia et al. 1981; Leatherland et al. 1991; Leatherland 1992). Leatherland did not rule out genetic differences due

to stock origin but suggested environmental agents as probable contributors to sexual precocity and the loss of sexual dimorphism. For example, since 1980, the percentage of precocious coho males in returning adults ranged from 40–60 percent in Lake Erie, whereas the percentage in British Columbia (from the same genetic stock) ranged from 2–5 percent (Leatherland et al. 1991). Lake Erie self-reproducing stocks also experience hermaphroditism. In other great waters, between 29 percent and 55 percent of the burbot (*Lota lota*) collected on the north coast of Bothnian Bay, Finland and Sweden, from 1987 to 1990 did not reach sexual maturity; between 87 percent to 98 percent near Tornio and Kemi were sterile (Pulliainen et al. 1992). This sterility was associated with irregular otolith growth and bone resorption. PCBs, DDT, dioxins, furans, and metals were quantified. The decline in striped bass from the San Francisco Bay delta was attributed to reduced waterflow and increased xenobiotics affecting egg production and egg and larval viability (Setzler-Hamilton et al. 1988). Reduced synthesis and resultant plasma/tissue levels of sex hormones (estradiol, progesterone, and testosterone) have been associated with elevated levels of cadmium, lead, BaP, PCBs, and mirex in sea stars (*Asterias rubens*), English sole, Atlantic cod (*Gadus morhua*), Atlantic croaker, rainbow trout, polychaetes (*Nereis virens*), and mussel (Voogt et al. 1987; Johnson et al. 1988; Freeman et al. 1982; Thomas 1988; Chen et al. 1986; Fries and Lee 1984; Kluytmans et al. 1988). Dall's porpoises (*Phocoenoides dalli*) from the northwest Pacific had reduced testosterone levels which were correlated with p,p'-DDE concentrations (Subramanian et al. 1987). PCB and DDE exposure through diet caused a reversible reduction in retinol and thyroxin and failure of embryo implantation in harbor seals (Brouwer et al. 1989). Freeman and Sangalang (1977) studied the adrenal and testicular effects of cadmium, arsenic, selenium, and Arochlor 1254 on grey seals (*Halichoerus grypus*). In this study, all of these xenobiotics altered normal steroid biosynthesis.

Harbor seals from declining and stable populations of the Wadden Sea exhibited significant reductions of plasma retinol and thyroid hormones (total and free thyroxin (T4), and triiodothyronine (T3)) when fed a diet of PCB-contaminated Wadden Sea fish. A six-month diet of relatively clean Atlantic mackerel (low PCBs) reversed the reduction. These field studies and parallel laboratory studies led the researchers to suggest that reduced plasma retinol and thyroid hormones from PCB exposure could increase susceptibility to infection by compromising the seals' immune systems (Brouwer et al. 1989). PCBs in the feral seals' fish diet were equivalent to 25 µg/kg body weight per day. The high-dose diet fed to confined seals was 1.5 mg PCB per day and 0.4 mg p,p'-DDE and the low-dose was 0.22 mg PCB and 0.13 mg p,p'-DDE. (Reijnders 1986; Brouwer et al. 1989).

Little evidence of ovarian activity was reported by Beland et al. (1992) in female beluga whales necropsied over the past 10 years. Thirty percent of the females were afollicular. Half of the 19 to 25 year old females had mammary lesions. One out of 20 male specimens was a true hermaphrodite.

Skewed sex ratios, reduced number of breeding males, female-pairing, and infertile supernormal clutches have been observed in Western and ring-billed gulls off the California coast and Puget Sound, herring gulls of the Great Lakes, and U.S. Caspian terns (*Hydroprogne caspia*) (Fox 1992; Fry et al. 1987; Fry and Toone 1981; Shugart et al. 1988). DDT and

methoxychlor injected into gull (*Larus californicus*) eggs caused reproductive tract modification of both sexes, and ovarian and oviduct tissue development in male embryos, effectively feminizing the embryo (Fry et al. 1987; Fry and Toone 1981). Fox (1992) projected that the feminization of male embryos from estrogenic agents such as DDT, mirex, TCDD, and methoxychlor occurred during peak contamination years (1972–1976) in Lake Ontario and Lake Michigan. Great Lakes herring gull endocrine disorders and reduced reproductive success (embryo and chick mortality, edema, development abnormalities, and aberrant nesting behavior such as female–female pairing) lessened with reduced contaminant levels (Gilbertson et al. 1991; Fox 1992; Mineau et al. 1984; Peakall and Fox 1987). Caspian terns on the Great Lakes continued to exhibit reduced reproductive success through the 80s, maintaining population levels only through recruitment from less contaminated Canadian colonies (Fox 1992; Gilbertson et al. 1991).

Laboratory And Mechanistic Studies

The hormones of the endocrine system convey chemical signals to distant parts of the body. Hormones influence cells by binding to specific cellular "receptors." Once bound to its receptor, the hormone–receptor complex becomes activated, and will alter the cell's activity (Figure 8). This is accomplished by influencing enzyme dynamics or inducing the expression of specific genes. Gene products may be enzymes that modify the cell's metabolism, structural proteins that will become part of the cell, or secretory materials. Hormones and their receptors are therefore potent moderators of cellular structure and function.

Xenobiotics influence the endocrine system through several mechanisms. Hormone levels in the blood can be affected by disruption or enhancement of their syntheses, and by increased metabolic breakdown via the MFO system. Alternately, the cellular receptors of hormones may be disrupted, making cells more or less responsive to hormonal signals. Dioxins are notorious for influencing levels of endogenous receptors. TCDD modulates receptors for glucocorticoids, prolactin, thyroxine, epidermal growth factor and estrogens (Umbreit and Gallo 1988).

This section will address xenobiotic effects on the endocrine system, including the thyroid, adrenal gland and pancreas. The disruptive influence of xenobiotics on these glands and their hormones is suspected to play a role in the wasting syndrome (Table 20). Xenobiotic effects on reproductive hormones will be discussed later.

Effects on the Thyroid

The thyroid produces two hormones, thyroxine (T_4) and triiodothyronine (T_3), which are involved in regulating cellular metabolism. Some of the xenobiotic substances known to affect thyroid hormone levels are DDT, dioxin, PCBs, toxaphene and lead (Chu et al. 1986; Tuppurainen et al. 1988). Disruption of thyroid homeostasis may be partly responsible for the wasting syndrome. Xenobiotics can both decrease (hypothyroidism) and increase (hyperthyroidism) thyroid activity, and, therefore, body metabolism. The effect observed depends on the dose and duration of exposure. For example, DDT can both inhibit and stimulate thyroid

activity, depending on dose. In pigeons, low doses of DDT produce hyperthyroidism, whereas high doses cause hypothyroidism (Jefferies 1975).

TCDD has alternate effects on the two thyroid hormones. Although thyroxine levels in the blood are depressed by TCDD, T_3 levels are generally increased, although reports vary (Muzi et al. 1987; Roth et al. 1988; Gorski et al. 1988b; Ivans et al. 1992). Thyroid stimulating hormone (TSH) from the pituitary stimulates release of both T_3 and T_4. Slight alterations in TSH levels have been reported following TCDD exposure (Henry and Gasiewicz 1987; Gorski et al. 1888a; Pohjanvirta et al. 1989a). However, the mechanism by which TCDD disrupts thyroid hormone concentrations is still poorly understood (Roth et al. 1988).

TCDD-induced alterations to thyroid hormones not only directly affect cell metabolism, but can influence the overall body metabolism as well. Brown adipose tissue (which regulates body temperature and weight through lipid and glucose metabolism) is secondarily affected by TCDD-induced decreases in T_4 (Weber et al. 1987; Rozman et al. 1987; Gorski et al. 1988b).

Unlike DDT and dioxin, PCBs and PBBs cause depression of both T_3 and T_4 levels in a dose-related manner in mammals. Marmoset monkeys orally dosed with 0.1, 1.0, and 3.0 mg/kg/day PCB exhibited reduced serum T_4 by 35, 81, and 99 percent, respectively (van den Berg et al. 1988a). However, the effects in birds appeared to be related to the length of exposure. PCB treatment of laying quail for 65-70 days resulted in depressed T_4 and T_3 concentrations, whereas prolonged exposure (120 days) increased plasma T_4 values (Grassle and Biessmann 1982).

The mechanism of PCB reduction in circulating thyroid hormones is two-fold. First, PCB congeners reduce levels of thyroid hormones in the blood by having a strong affinity for T_4 binding sites in prealbumin, the plasma transport protein for T_4 (Rickenbacher et al. 1986). Second, production of T_3 and T_4 in mammals is reduced due to direct damage to the thyroid gland (Byrne et al. 1987; van den Berg et al. 1988a, b). There is not an increase in thyroid hormone catabolism by the liver or other tissues (Byrne et al. 1987).

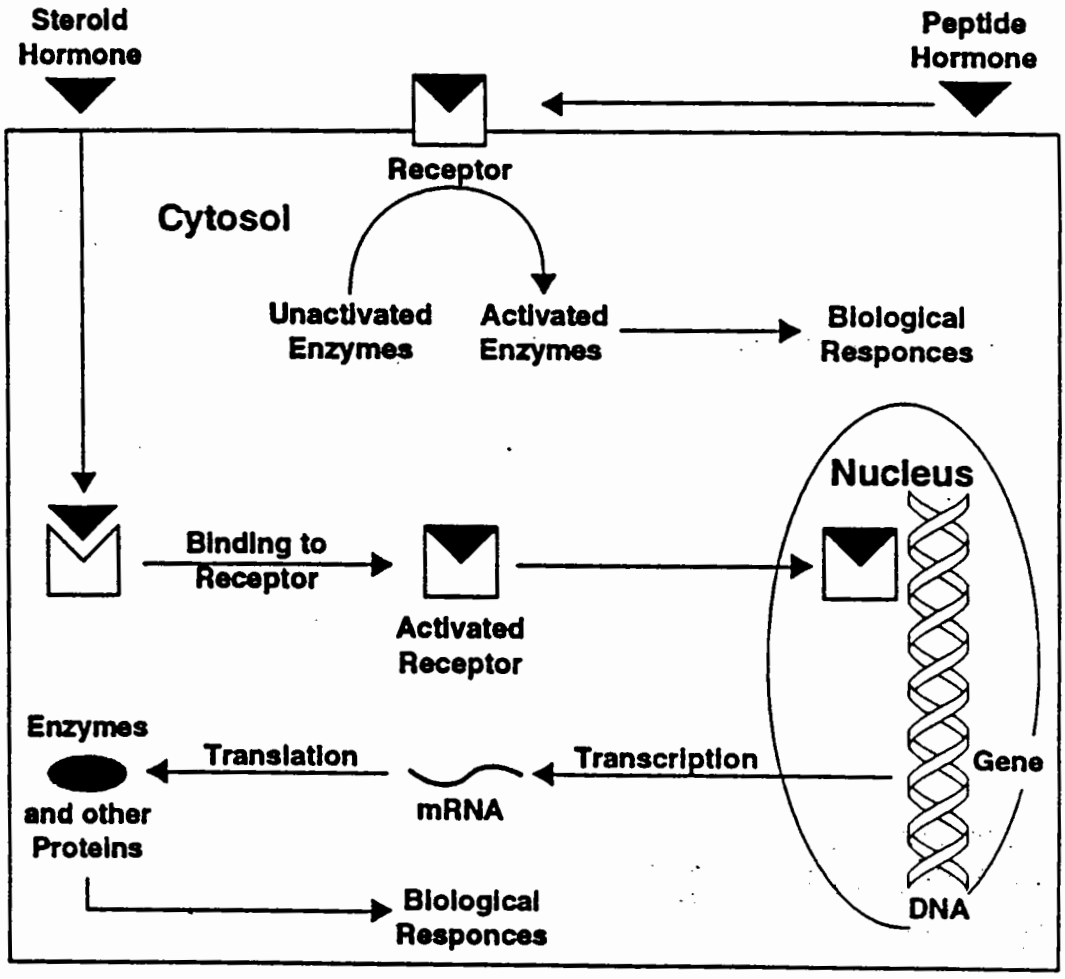
Other xenobiotic substances can also disrupt adrenal gland function. Toxaphene inhibited corticosterone synthesis in the rat adrenal cortex (Mohammed et al. 1985). Veltman and Maines (1986) found that 30 µmol/kg mercuric chloride caused a 50 percent increase in MFO activity in rat adrenal glands, causing subsequent disruption in serum levels of adrenocortical hormones.

Effects on the Pancreas

Two hormones from the pancreas, insulin and glucagon, regulate glucose concentrations in the blood. Hyperglycemia results from decreases in insulin, allowing blood sugar levels to rise. The alternate, hypoglycemia, is due to decreased blood sugar. TCDD decreased insulin and glucagon in rats (Gorski et al. 1988) and insulin in rabbits (Ebner et al. 1988), resulting in transient hyperglycemia. In guinea pigs, insulin concentration was depressed for 10 days following 1 mg/kg TCDD treatment (Brewster and Matsumura 1988). However, TCDD-induced

FIGURE 8

MECHANISM OF HORMONE–RECEPTOR ACTION



Mechanism of hormone action through cellular receptors. Peptide hormones attach to membrane–bound receptors. The hormone–receptor complex activates enzymes, altering cellular processes. Unlike peptide hormones, steroid hormones readily enter the cell. Once bound, the hormone–receptor complex is activated and may interact with specific genes, inducing transcription to form mRNA. The mRNA is translated in the cytosol to produce enzymes and other proteins, eliciting a biological response.

TABLE 20

MECHANISMS IMPLICATED IN THE WASTING SYNDROME

TARGET ORGAN	MECHANISM	PROCESS AFFECTED
Liver	Mixed-function Oxidase System	Carbohydrate Metabolism
Brain	Neurotransmitters	Feeding Behavior
Thyroid	Thyroxine & Triiodothyronine	Cellular Metabolism Brown Fat Metabolism
Adrenal Gland	Corticosterone	Gluconeogensis
Pancreas	Insulin & Glucagon	Blood Glucose Levels

Effects on the Adrenal Glands

Corticosterone from the adrenal cortex is an important hormone in gluconeogenesis (formation of new glucose molecules). Corticosterone levels were elevated 5–7 times normal values in rats following TCDD treatment (Gorski et al. 1988a; Pohjanvirta et al. 1989a). Adrenalectomy of rats drastically increased TCDD-induced mortality in rats (Gorski et al. 1988c), whereas corticosterone-replacement reduces mortality to nonadrenalectomized levels. Corticosterone, therefore, provides partial protection from TCDD-induced toxicity in rats resulting from reduced gluconeogenesis (Gorski et al. 1990).

Some of the effects of dioxins on adrenal hormones are mediated through receptor disruption. TCDD treatment produces an approximately 30 percent decrease in binding capacities of hepatic glucocorticoid receptors in female mice (Stohs et al. 1990; Lin et al. 1991b). This effect does not appear to be regulated by the Ah locus. In rat liver, the dioxin and glucocorticoid receptors are virtually indistinguishable physico-chemically (Cuthill et al. 1988).

Production of corticosterone is controlled by adrenocorticotropic hormone (ACTH) from the pituitary gland. Hypothysectomized rats suffer greater TCDD-induced toxicity, which is returned to "normal" following administration of corticosterone (Gorski et al. 1989d), suggesting a role of ACTH in dioxin toxicity. However, alterations of serum corticosterone levels are due to altered responsiveness of the adrenal to ACTH simulation rather than to changes in plasma ACTH levels (Jefcoate et al. 1987; DiBartolomeis et al. 1987; Moore et al. 1989). Kerkvliet et al. (1990a) demonstrated that elevation of corticosterone in mice exposed to either TCDD or PCBs is dependent on the Ah receptor.

hypoglycemia preceded insulin depression, indicating a period of insulin hypersensitivity (Gorski and Rozman 1987). TCDD administration to rats further resulted in hypersensitivity to the satiating effects of glucose and fructose (Pohjanvirta and Tuomisto 1990a). These effects on pancreatic hormones may also play a role in the wasting syndrome by altering serum glucose levels and peripheral satiety signals.

2.2.5.7 Reproductive Impairment

Wildilife Studies

A number of top predator species have exhibited reproductive problems or population declines in a number of areas in the Great Lakes basin since the 1950s. This list includes birds (the bald eagle (*Haliaetus leucocephalus*) (Postupalsky 1971a, b; IJC 1988), black-crowned night-heron (Gilbertson personal communication 1988), Caspian tern (Kurita et al. 1987), common tern (Gilbertson 1974a; Connors et al. 1975; Custer et al. 1988), double-crested cormorant (Postupalsky 1976; Weseloh et al. 1983; Ludwig 1984), Forster's tern (Kubiak et al. 1989; Kubiak and Harris 1985), herring gull (Keith 1966; Ludwig and Tomoff 1966; Gilbertson 1974b; Mineau et al. 1984; Mineau and Weseloh 1981), osprey (*Pandion haliaetus*) (Berger and Mueller n.d.; Postupalsky 1971a, 1980, 1983, 1985), and ring-billed gull (Sileo et al. 1977)), mammals (the Beluga whale (Reeves and Mitchell 1984; Sergeant 1986; Beland et al. 1988; Pippard 1985), mink, and otter (*Lutra canadensis*) (Pils 1987)); fish (the lake trout (Mac et al. 1985, 1988)); and reptiles (the snapping turtle ((*Chelydra serpentina*)) (Brooks 1987). All of the above animals depend upon Great Lakes fish for their food source. Researchers found relatively high concentrations of organochlorine compounds, pesticides, and industrial chemicals in the tissues of animals and their eggs in the affected populations (Ludwig and Tomoff 1966; Gilman et al. 1977; Gilbertson and Fox 1977; Gilman et al. 1978; Frank et al. 1979; Haseltine et al. 1981; Hallett et al. 1982). Disorders which affect the success of reproduction in the animals included reduced fertility, reduced hatchability, reduced viability of offspring, impaired hormone activity, or changed adult sexual behavior (described in the previous section on endocrine disruption).

Common effects which characterize the current reproductive situation in the Great Lakes are as follows:

- high tissue concentrations of PCBs, DDE, dieldrin, and/or other organochlorine chemicals
- embryo toxicity and/or wasting
- offspring or embryo deformities
- adult parental behavioral change
- shoreline populations sparser than inland populations.

Scientific certainty in linking the observed effects with specific toxic chemicals has been difficult due to the various analytical methods employed; numerous endpoints of effect; species, age, and sex differences; and potential interactions between chemicals. Analagous evidence, such

as observation of similar symptoms across a wide variety of organisms and contamination-linked geographic locations, is often used to link contaminants with effects (Tillitt et al. 1992). In a recent study which evaluated PCB residues in double-crested cormorant eggs, Tillitt et al. (1992) statistically linked the observed reproductive effects (egg mortality) with PCBs measured as dioxin equivalents (TCDD-EQ) using the H4IIE rat hepatoma cell bioassay. This study demonstrated the relative enrichment in PCB potency in the Great Lakes environment which may explain 1) the observed variable reproductive success and 2) the continued adverse effects in the populations, even though total PCBs have declined in the environment.

Eggshell thinning effects and accompanying reproductive loss as a result of DDT and its metabolites were well-publicized in the 1960s and 1970s. As ambient levels of DDT declined, many of the Great Lakes populations recovered. However, populations utilizing certain geographical locations continue to exhibit reproductive failure (Peakall and Fox 1987; Peakall 1988; Fox et al. 1991; Harris 1988). In particular, areas of Lake Michigan, Lake Ontario, Lake Superior, and Lake Huron remain affected by the contaminants of concern; Green Bay (Lake Michigan), Saginaw Bay (Lake Huron), and Hamilton Harbor (Lake Ontario) are the most influenced (Government of Canada 1991). Reproductive problems continue in seven species of Great Lakes birds, including the herring gull, ring-billed gull, common tern, Caspian tern, Forster's tern, black-crowned night-heron, bald eagle, double-crested cormorant, great blue heron (*Ardea herodias*), and the Virginia rail (*Ralus virginianus*) (Government of Canada 1991).

Since 1980, double crested cormorants and ring-billed gulls numbers increased (Blokpoel and Tessier 1986; Blokpoel 1988), although bald eagles, common terns, mink, and otters failed to recover. Recent studies which compared Great Lakes inland versus shoreline bald eagle populations found significantly lower reproductive success in shoreline nests (Bowerman et al. 1991; Kubiak and Best 1991). The shoreline nests contained addled eggs with lethal concentrations of PCBs, DDE, and dieldrin; 1987-1988 nestlings contained six times the PCB and DDE plasma levels as did nestlings from the inland nests. Bald eagle productivity was negatively correlated with PCB, DDE, and dieldrin load with the 1986-1990 breeding rate (0.6 young/occupied nest) too low to maintain a stable population (Bowerman et al. 1991). Poor Great Lakes shoreline reproduction or sparseness of populations has also been observed in Forster's, common, and Caspian terns, mink, and river otters (Gilman et al. 1991; Government of Canada 1991; Gilbertson et al. 1991). Correlations found between the hatching success of the common snapping turtle and contaminated wetlands location between 1986 and 1989 demonstrate the persistence of effects and locational proximity (Bishop et al. 1991).

In order to maintain a stable bald eagle population, eagle eggs cannot exceed 3.5 ppm DDE (Weimeyer et al. 1984), and, at 15 ppm DDE, populations of bald eagles suffer 100 percent loss of productivity. Addled eggs collected in the Great Lakes basin between 1986 and 1990 held 3.4 to 20.5 ppm DDE (Kubiak and Best 1991) (Table 21).

Domestic mink fed Saginaw Bay carp contaminated with PCBs responded in a dose-response manner in reproductive capability (number of offspring, kit body weight, and organ weight) and kit survivability (Heaton et al. 1991). Wren et al. (1987) reported a syngergistic

TABLE 21

MEASURES OF PRODUCTIVITY AND ADDLED EGG RESIDUES:

MICHIGAN, OHIO, AND ALASKA, 1986 - 1990

Lake Basin/Region	Addled Egg Residues[1] (µg/g Fresh Wet Weight)			Productivity[2]	
	PCBs	p,p'-DDE	Dieldrin	Prod. 1[3]	Prod. 2[4]
Lake Huron	76.7	20.5	1.16	0.59	41.2
Lake Michigan	41.0	20.1	1.32	0.68	48.0
Lake Erie	22.1	3.4	0.43	0.75	52.6
Lake Superior	10.1	4.5	0.25	0.84	55.4
Inland Ohio	10.7	1.9	0.19	0.71	57.1
Inland Mich.-U.P.	7.5	3.2	0.24	0.93	59.7
Inland Mich.-L.P.	8.2	2.7	0.11	1.14	71.8
Interior Alaska	1.4	0.5	0.02	1.29	76.8

[1] Residues from 46 eggs collected from 36 breeding areas.
[2] Productivities based on outcomes of 886 occupied breeding areas.
[3] Number of fledged young per occupied breeding area.
[4] Percent success rate of occupied breeding areas.

effect of methylmercury and PCB on mink kit growth and survival which exceeded the reduced growth rate observed in kits exposed to 1.0 µg/g PCB in mothers' breast milk. These experiments were conducted with mercury and PCB concentrations similar to those found in some regions of the Great Lakes.

The reproductive success of the declining white croaker (*Genyonemus lineatus*) was shown to be affected in spawning studies from a contaminated California site (San Pedro Bay) compared to a reference site (Dana Point) (Hose et al. 1989). Ability to spawn, reduced fecundity (by 32 percent), reduced fertility (by 14 percent) and early oocyte loss (greater than 30 percent) were associated with ovarian DDT concentrations. No fish with greater than 3.8 ppm DDT spawned;

36 percent of the San Pedro sample had greater than 4 ppm ovarian DDT. Contaminant levels (total DDT plus PCBs) in the sea-surface microlayer were found toxic to pelagic fish eggs and larvae in this same area (Cross et al. 1987).

Mercury also impacts reproductive potential in both sexes. High rates of fetal mortality result from *in utero* exposure during organogenesis (Eccles and Annau 1987). Pheasants treated with mercury exhibited reduced egg production, hatchability and egg weight, and even production of shell-less eggs (Fimreite 1971). Treatment of female mice with a single dose of methylmercury resulted in increased losses in pre- and early post-implantation fetuses (Verschaeve and Leonard 1984). Oral dosing of squirrel monkeys with 50 or 90 µg/kg methylmercury for three months increased frequency of reproductive failure, decreased birth weight and impaired offspring behavior (Burbacker et al. 1984). Mercury is present in breast milk and crosses the placenta (Eccles and Annau 1987; Peterle 1991; Yoshida et al. 1992; Urbach et al. 1992). Spermatogenesis is impaired in mice injected with 1 mg/kg methylmercury (Lee and Dixon 1975). *In vitro* treatment of monkey sperm decreases sperm motility (Mohamed et al. 1986a, b).

Kahn and Weis (1987) found differential resistance in the mummichog (*Fundulus heterclitus*) from a mercury-polluted creek compared to a clean creek, as exhibited by reduced fertility success attributed to changes in sperm motility. Inorganic mercury caused a significant decrease in the fertility of the fish and offspring from the polluted creek, whereas highly toxic methyl mercury (MeHg) did not. The reverse was seen in the control fish from the clean creek. Susceptibility to inorganic mercury was attributed to the physiological cost of developing pollutant tolerance, i.e., the inability to withstand further stress (Kahn and Weis 1987; Rahel 1981). Using sperm cell motility in the American sea urchin (*Arbacia punctulata*) as an index for cell toxicity, Nelson (1990) demonstrated a biphasic dose-response in sperm motility following exposure to paraoxon and dieldrin; sperm motility was inhibited by lindane; and stimulated by mirex.

Reproductive effects in the endocrine system of marine animals have been associated with heavy metals, atrazine, and chlorinated hydrocarbons such as PCBs, DDT, lindane, and carbofuran (Sukumar and Karpagaganapathy 1992; Reijnders and Brasseur 1992; Reijnders 1986; Simic et al. 1991; Batty 1990). Carbofuran exposure resulted in atretic oocytes, retrogressive ovaries, oocyte-depleted germinal vesicles, and reduced yolk granules in fresh-water fish (*Colisa alia*) (Sukumar and Karpagaganapathy 1992). Uterine occlusions and stenoses, bilateral adrenocortical hyperplasia, and hormonal osteoporosis observed in pinnipeds were associated with PCBs and DDT (Baker 1989; Bergman and Olsson 1985; Brouwer et al. 1989; Helle et al. 1976a, b; Reijnders 1986; Reijnders and Brasseur 1992). Cadmium, lead, and PCBs have affected biosynthesis of reproductive hormones in other marine animals as described in the previous section on endocrine disruption (den Besten 1991; Freeman et al. 1982; Johnson et al. 1988; Voogt et al. 1987; Thomas 1988).

Information regarding contaminant effects on humans are limited primarily to studies of contamination from occupational disasters, cohort studies, and clinical reports described in Section 2.2.5.8 (Fein et al. 1984; Rogan et al. 1986; Rogan et al. 1988; Jacobson et al. 1990; Jacobson and Jacobson 1991; Leoni et al. 1989; Bush et al. 1986). In recent years, a number of studies have linked reproductive changes in humans with ambient exposure. For example, findings from studies of the Michigan Maternal/Infant Cohort associated reproductive effects (low birth weight, shorter gestional age, smaller head circumference) with the lifetime experience of the mothers' Lake Michigan fish consumption (Jacobson et al. 1990; Jacobson and Jacobson 1991). Bush and coworkers (1986) found an association between the presence of three PCB congeners: (2,3,4,2',4',5'– IUPAC No. 153, 2,3,5,2',3',4'– IUPAC No. 137 and 2,4,5,3',4'– IUPAC No. 123 and loss of sperm motility in males with fertility problems. Carlsen et al. (1992), in a meta–analysis of sperm count studies dating back to 1938, found an approximate 50 percent reduction in sperm count and a significant decrease in seminal fluid volume in men worldwide between 1938 and 1991. Genetic changes were ruled out since the change was worldwide over one generation. Among his suggestions for why sperm numbers have declined, Sharpe (1992) points out that exposure to DDT, PCB, and other chemicals capable of disrupting the endocrine system during a critical window of time in early intra–uterine development can affect the production of spermatogonia. This hypothesis is supported by the timing of the chemical revolution since World War II and the concomitant decrease in sperm count in male humans.

Laboratory And Mechanistic Studies

Some of the most insidious effects of airborne water pollutants are those on reproduction. Reproductive impairments are largely due to endocrine disruption. Xenobiotic compounds can affect endocrine regulation of reproduction by a variety of means, including disrupting pituitary control of reproductive cycles, altering metabolic synthesis or breakdown of hormones, mimicking natural endogenous hormones, and antagonizing or blocking hormonal signals.

The levels of steroids in both males and females, as well as their reproductive cycles, are regulated by peptide hormones, such as luteinizing hormone (LH) from the hypothalamus. LH stimulates production of sex steroids (estrogen, progesterone, and testosterone) by the gonads, and is regulated by gonadotropin–releasing hormone (GnRH) from the hypothalamus. Males and females exhibit differences in their pattern of LH secretion. Females release LH in a pulsatile manner and exhibit a surge of LH secretion that stimulates ovulation of eggs from the ovary. Males produce relatively constant quantities of LH, and are not capable of producing an LH surge. These patterns are established during embryonic development, or shortly following birth.

Some toxic substances can drastically alter reproductive function by disrupting LH secretion from the pituitary, thereby upsetting the reproductive regulatory center. TCDD decreases GnRH receptors in the pituitary of male rats, thereby reducing the pituitary's responsiveness to androgen deficiency and preventing compensatory increases in LH secretion (Bookstaff et al. 1990). Other compounds, such as DDT, DDE and parathion, also decrease LH levels in adults (Gellert et al. 1972; Richie and Peterle 1979; Rattner et al. 1984; Rattner et al. 1982a, b; Rattner and Ottinger 1984). Single dose exposure of pregnant mice to 0.16 μm/kg

TCDD feminize LH secretory patterns in her male offspring as adults (Mably et al. 1992). By altering levels of LH, or its pattern of secretion, xenobiotics significantly impair reproduction in both males and females.

Another pituitary hormone involved with reproduction is prolactin, which stimulates production of milk in female mammals and influences reproductive functions in other vertebrate groups. Many different xenobiotics have been demonstrated to disrupt serum prolactin concentrations. Prolactin levels were altered in ring doves fed diets containing a mixture of DDE, PCB, and mirex (McArthur et al. 1983). TCDD significantly reduces serum prolactin concentrations in rats within 4 hours of treatment (Jones et al. 1987; Russell et al. 1988; Moore et al. 1989). This effect is correlated with a dramatic increase in dopamine in the brain (Russell et al. 1988). Circadian alterations of prolactin secretion (Jones et al. 1987) may be influenced by TCDD-induced alterations in melatonin release (Linden et al. 1991). TCDD also alters levels of prolactin receptors in many tissues. Seven days following TCDD treatment, hepatic prolactin receptors are reduced by 78 percent in liver, but increased to 191 percent in kidney (Jones et al. 1987).

Xenobiotic compounds can alter levels of endogenous hormones. PCBs disrupt levels of the pregnancy-maintaining hormone progesterone in monkeys (Truelove et al. 1990). PCBs also cause increased levels of estrogens and prostaglandins during pregnancy (Lundkvist and Kindahl 1989). Androgen deficiency induced by TCDD treatment in rats may be the result of a decrease in testosterone secretion by the testicles (Moore and Peterson 1988).

An important mechanism for altering steroid hormone levels is through the MFO system. Several MFO enzymes are involved in the biosynthesis of sex steroids (Table 22). All steroids are derived from cholesterol, and many serve as substrates for the formation of others. For instance, the female steroid progesterone is utilized by males to make testosterone, and females use testosterone as a necessary building block for estrogens. Other MFOs eliminate sex steroids by oxidizing them to forms readily excretable by the kidneys. The MFO system is, therefore, integral in the regulation of sex-steroid levels in the blood, either by their synthesis, interconversion of one form to another, or by metabolism into waste products that are eliminated from the body. By inducing the MFO system, xenobiotics are able to drastically alter levels of sex steroids in the body (Dieringer et al. 1979; Truscott et al. 1983; Gustafsson et al. 1983; Khan 1984; Payne et al. 1987). Xenobiotics may induce some MFO enzymes but inhibit others (Voorman and Aust 1987, 1989). The inhibition of estradiol hydroxylase activity by TCDD (Voorman and Aust 1989) may help explain the TCDD-induced increase in estrogen levels (Gallo 1988). Examples of MFO induction and its reproductive effects either by hydrocarbons or specific xenobiotics are presented in Table 23 and Table 24, respectively.

Many xenobiotics mimic natural hormones. DDT is an artificial estrogen, and probably the best studied example of an exogenous hormone mimic (Bulger and Kupfer 1983; McLachlan 1985). The earliest laboratory account of the estrogenic nature of DDT was the discovery that DDT was uterotropic (increased uterine weight) in rats (Leven et al. 1968; Welch et al. 1969). Further, mice exposed to DDT exhibited prolonged estrous cycles and decreases in ova

implantation (Lundberg 1973). It was subsequently established that the o,p'-isomer of DDT was largely responsible for the uterotropic activity (Welch et al. 1969). DDT binds to the cellular estrogen receptor and initiates the same sequence of events as natural estrogen (Nelson 1974), including an increase uterine DNA synthesis (Ireland et al. 1980) and induction of protein synthesis and secretion (Stancel et al. 1980). Many of these induced proteins are enzymatic in nature (Singhal et al. 1970; Cohen et al. 1970; Kaye et al. 1971; Bulger et al. 1978b; Bulger and Kupfer 1978, 1983b). Particularly notable, one of the proteins induced by o,p'-DDT in the rat uterus is the receptor molecule for another sex steroid, progesterone (Mason and Schulte 1980).

Other xenobiotics are also hormone mimics. PCBs have extensive effects on reproductive systems (Reijnders 1988), including stimulation of uterine weight increases, prolonged estrous cycles, impaired fertility, reduced number of young, and reduced maternal ability to carry young to term (Table 25). These effects are mediated in part by PCBs ability to bind to uterine estrogen receptors (Korach et al. 1988). PCBs also bind to other receptors in the rat liver (Buff and Brundl 1992), possibly interfering with the function of these endogenous receptors, which also bind the thyroid hormones thyroxine and triiodothyronine. Some of TCDD's estrogenic properties may be due to its ability to bind to estrogen receptors (Umbreit et al. 1989b).

Some xenobiotics only mimic endogenous hormones after being metabolized, or activated, in the body. Methoxychlor (bis-p-methoxy DDT) is a proestrogen and is metabolized by the hepatic MFO system into estrogenic products (Nelson et al. 1976, 1978; Budger et al. 1978c; Ousterhout et al. 1979, 1981). The estrogenic metabolite of methoxychlor (HPTE) was shown to be about 10 times more active than o,p'-DDT (Ousterhout et al. 1981). See Table 26 for the estrogenic effects of methoxychlor on reproduction.

Xenobiotics may also block or reduce the activity of endogenous hormones. Many of these have antiestrogenic effects in females, such as a decrease in: 1) uterine weight, 2) cell growth, 3) estrogen-induced protein secretion, 4) estrogen and progesterone receptors, 5) peroxidase activity, 6) estrogen-stimulated c-fos oncogene mRNA, 7) epidermal growth factor receptor binding activity, and 8) EGF mRNA levels (Table 27). Antiestrogenic compounds can impair female reproductive capacity, including the ability to conceive, maintain young throughout pregnancy, deliver, and care for young postnatally.

There are several mechanisms for these antiestrogenic effects. TCDD directly reduces the concentration of estradiol-17ß in human tissues by increasing the metabolism of estradiol to a less active form (Graham et al. 1988; Gierthy et al. 1987; Spink et al. 1990; Spink et al. 1992). The antiestrogenic effect of TCDD in many cases is mediated not by reductions in estrogen, but by its ability to down-regulate estrogen receptors (Romkes et al. 1987; Umbreit and Gallo 1988; DeVito et al. 1992). Ten nM TCDD can cause up to a 74 percent decrease in estrogen receptor levels in mouse cells in 6 hours (Zacharewski et al. 1991), and a 63 percent decrease in human cells by 12 hours following treatment (Harris et al. 1990). Estrogen receptor down-regulation is dependent upon dioxin binding to the Ah receptor (Gasiewicz and Rucci 1991). In normal circumstances, estradiol mediates some of its effects through small, regulatory proteins called growth factors. For example, estradiol induces receptors for epidermal growth factor (EGF).

TCDD inhibits estradiol's induction of EGF receptors (Astroff et al. 1990; Safe et al. 1991; Abbot et al. 1992). The TCDD-induced decreases in both estrogen and growth factor receptors are mediated through the aryl hydrocarbon (Ah) receptor (Zacharewski et al. 1991, 1992; Lin et al. 1991a, b; Abbot et al. 1992; Schrenck et al. 1992).

In males, xenobiotics may exhibit estrogenic or antiandrogenic activities (Table 28). Effects include testicular atrophy, reduced fertility and arrested spermatogenesis. Reduced levels of androgens are related to both decreased secretion from the testes and increased metabolism via induction of the MFO system.

TABLE 22

STEROID HORMONE SYNTHESIS BY MIXED-FUNCTION OXIDASES

CYTOCHROME	SUBSTRATE	PRODUCT
$P450_{scc}$	Cholesterol	Pregnenolone
$P450_{17alpha}$	Progesterone	Testosterone
$P450_{XIX}$ family (Aromatase system)	Testosterone	Estradiol
$P450_{21}$ and $P450_{11beta}$	Progesterone	Cortisol, Corticosterone, and Aldosterone

Source: Fevold 1983; Nebert and Gonzalez 1987; Simpson and Waterman 1989

TABLE 23

EFFECTS OF HYDROCARBONS ON MFO INDUCTION AND REPRODUCTIVE IMPAIRMENT

SPECIES	EFFECTS	REFERENCE
Cunners	No evidence for altered steroid metabolism	Hellou & Payne 1986
Chicken	MFO induction in kidney	Lee et al. 1986
Herring gulls	MFO induction in kidney	Lee et al. 1985
Salmon	Increased levels of sex steroids in bile	Truscott et al. 1984
Flounder	Inverse relationship between MFO induction and fertilization success	Spies et al. 1984
Herring gulls	MFO induction	Gorsline et al. 1981
Mallard ducks	MFO induction	Miller et al. 1978
Trout	No evidence for reproductive impairment	Hodgins et al. 1977

TABLE 24

EFFECTS SPECIFIC XENOBIOTICS ON MFO INDUCTION AND REPRODUCTIVE IMPAIRMENT

COMPOUND	SPECIES	EFFECTS	REFERENCE
TCDD	Rat	Decreased plasma testosterone and dihydrotestosterone by 90 percent and 75 percent, respectively	Moore et al. 1985
TCDD	Rat	Decreased estradiol	Gierthy et al. 1987
TCDD	Rat	Decreased androgen concentrations, reduced sex glands and reproductive capacity	Sager 1983
DDT	Rat	Induced MFO enzymes that metabolize androgens	Haake et al. 1987
PCBs	Pigeon	Induced several P450 isoforms	Borlakoglu et al. 1991
PCBs	Salmon & Flounder	Decreased androgen concentration	Truescott et al. 1983
PBBs	Rat	Increased steroid catabolism	McCormack et al. 1979
HCB	Rat	Induced MFO enzymes that metabolize androgens	Haake et al. 1987
Mercury	Rat	Induced of MFOs and alteration of adrenal steroid metabolism	Veltman and Maines 1986

TABLE 25

REPRODUCTIVE EFFECTS OF POLYCHLORINATED BIPHENYLS

SPECIES	EFFECTS	REFERENCE
Rhesus monkey	Altered progesterone levels and increased duration of menses	Truelove et al. 1990
Guinea pig	Increased levels of estrogens and prostaglandins	Lundkvist and Kindahl 1989
Marmoset monkey	Absence of corpora lutea	van den Berg et al. 1988b
Mourning dove	Altered progesterone levels and reduced reproductive success	Koval et al. 1987
Mink	Decreased number of young	den Boer 1983
Japanese quail	Decreased plasma estradiol levels before sexual maturity, delayed oviposition and diminished laying capacity	Biessmann 1982
Mink	Decreased number of young	Jensen et al. 1977
Rhesus Monkey	Impaired fertility and ability to carry infants to term	Allen and Barsotti 1976
Rat	Decreased number of young	Linder et al. 1974
Mouse	Prolonged estrous cycle	Orberg and Kihlstroem 1973
Fish	Reabsorption of egg sac	Mac et al. 1988

TABLE 26

REPRODUCTIVE EFFECTS OF METHOXYCHLOR

SPECIES	EFFECTS	REFERENCE
Mouse	Induced steroid secretion by ovarian cells	Martinez and Swartz 1992
Mouse	Stimulation of uterus & its secretions indistinguishable from that of estradiol	Rourke et al. 1991
Mouse	Stimulated uterine hypertrophy	Eroschenko 1991
Mouse	Increased uterine weight	Eroschenko and Cooke 1990
Rat and Hamster	Induced behavioral estrus	Gray et al. 1988
Cells	Metabolites of methoxychlor are potent estrogens	Kupfer and Bulger 1987
Rat	Methoxychlor is a proestrogen	Bulger et al. 1978c
Rat	Methoxychlor binds to uterine estrogen receptors	Nelson 1974
Rat	Methoxychlor 16 times less estrogenic than o,p'– DDT	Bitman and Cecil 1970
Mouse	Methoxychlor is a proestrogen	Kapoor et al. 1970
Rat	Increased uterine weight	Welch et al. 1969

TABLE 27

ANTIESTROGENIC EFFECTS OF XENOBIOTICS IN FEMALES

COMPOUND	SPECIES	EFFECTS	REFERENCE
TCDD	Rat	Decreased: uterine weight; estrogen & progesterone receptors; EGF binding; and enzyme activity	Dickerson et al. 1992
TCDD	Mouse	Inhibited estrogen-induced EGF receptors	Abbot et al. 1992
TCDD	Rat	Decreased: uterine weight; estrogen & progesterone receptors; EGF binding and receptors; c-fos mRNA levels; and enzyme activity	Safe et al. 1991
TCDD	Rat	Decreased: uterine weight; estrogen, progesterone and EGF receptors; EGF mRNA levels; and enzyme activity	Astroff and Safe 1991
TCDD	Rat	Decreased c-fos mRNA levels	Astroff et al. 1991
TCDD	Human cells	Altered secretion of estrogen-induced proteins	Biegel & Safe 1990
TCDD	Rat	Decreased uterine EGF receptor binding activity and EGF receptor mRNA	Astroff et al. 1990
TCDD	Hamster, guinea pig, rat	Altered estrogen metabolism	Umbreit et al. 1989a
TCDD	Mouse	Depressed estrogen-induced uterine weight gain	Umbreit et al. 1988
TCDD	Pike	Retarded egg development and fry growth	Helder 1980
Lindane	Rat	Delayed vaginal opening, disrupted cycles, reduced uterine weight	Chadwick et al. 1988
Lindane	Rat	Ovarian atrophy and impaired oogenesis	van Giersbergen et al. 1986

In some cases, the mechanism of action remains obscure, even after extensive research. An example is the effect of DDE (an analog of the pesticide DDT) on eggshell thickness in birds. Ratcliffe (1967) was the first to report the toxic effects of substances on eggshell weights. Mallard hens fed 50 ppm DDT produced eggshells that were 18 percent thinner and weighed 12 percent less (Kolaja and Hinten 1979). Both alteration in metabolism of steroids (Peakall 1967; 1970a, b; Lustick et al. 1973; Peterle et al. 1974; Haegele and Tucker 1974) and impairment of steroid binding to cellular receptors (Lundholm 1987) have been reported in birds exposed to DDE. Alterations in levels of parathyroid hormone (which is involved in regulating calcium concentrations) may be involved in eggshell thinning (Parsons and Peterle 1977; Haseltine et al. 1981). DDT and DDE also are potent inhibitors of calmodulin, a cellular protein important for proper deposition of eggshell calcium (Lundholm 1987). However, in spite of intensive investigation, the exact mechanism by which DDE reduces eggshell thickness is still poorly understood (Peterle 1991).

Xenobiotic contaminants cause numerous effects on developing young (see Transgenerational Effects, Section 2.2.5.8). Xenobiotics both cross the placental barrier (van den Berg et al. 1987) and are transferred to newborns via breast milk (Courtney and Andrews 1985). In pheasants, 1 percent of TCDD administered to the female is incorporated into each of her first 15 eggs (Nosek et al. 1992). Further, TCDD is known to reduce transfer of placental nutrients to developing young (Manchester et al. 1987), thereby impairing development.

2.2.5.8 Transgenerational Effects

An increasing body of evidence describing the effects of low-level, chronic exposure to twentieth century chemicals has caused toxicologists to expand their perspective of concern from impacts on the exposed organism to consideration of effects on the progeny born to the originally exposed individual. In many cases, the parent organism is apparently unaffected by the exposure, but serves only as an accumulator of contaminants, ultimately exposing the offspring where an effect may occur. The health impacts resulting from the exposure of progeny secondarily to the original parentally acquired contaminants are referred to as a transgenerational effects. In humans, this secondary exposure of the progeny can take two forms: (1) *in utero* exposure prior to parturition or hatching, and (2) postpartum exposure of the newborn via breast milk.

Approximately 25 chemical substances are known to produce transgenerational effects in humans, while over 800 are known to do so in laboratory animals (Kurzel and Cetrulo 1981). The reasons for this discrepancy include both the fact that humans are more resistant to some of these substances, and that subtle alterations or deficits in neuromuscular maturity, body weight, physical size, autonomic regulation, behavioral endpoints, and the like have only recently begun to be investigated (Fein et al. 1983; Jacobson et al. 1992).

With respect to *in utero* exposure of the human, there are three developmental periods during which the unborn child is at risk of impairment (Kurzel and Cetrulo 1981). These developmental periods, summarized in Table 29, are: (1) fertilization and implantation, (2) the embryonic period, and (3) the period of fetal development.

TABLE 28

ESTROGENIC AND ANTIANDROGENIC EFFECTS OF XENOBIOTICS IN MALES

COMPOUND	SPECIES	EFFECTS	REFERENCE
TCDD	Rat	Decreased androgen secretion	Moore and Peterson 1988
TCDD	Rat	Reduced testosterone 90 percent, dihydrotestosterone 75 percent, and reduced testis and epididymis weights	Moore et al. 1985
PCB	Rat	Increased testis weight	Johansson 1987
DDT	Rat	Induce MFO enzymes that metabolize androgens	Haake et al. 1987
DDT and Methoxychlor	Rat	Bind to testicular estrogen receptors	Bulger et al. 1978a
DDT	Rat	Blocks androgen binding to prostate receptors	Wakeling and Visek 1973
Lindane	Rat	Inhibited spermatogenesis, seminiferous tubules degenerated	Chowdhury et al. 1987
Lindane	Rat	Estrogenic effect, including atrophic testes and spermatogenic arrest	van Velson et al. 1986
Lindane	Rat	Estrogenic effect	van Giersbergen et al. 1984
HCB	Rat	Induce MFO enzymes that metabolize androgens	Haake et al. 1987

Aside from the small percentage of morphologic abnormalities, or birth defects, attributable to chemical contaminants — estimated to be 4–6 percent of all birth defects (Kurzel and Cetrulo 1981) — the majority of the observed effects will be associated with the fetal development period.

In this period, toxic effects are usually manifested in a diminution of cell size or a reduction in cell numbers. Since this developmental phase represents a period of unprecedented growth and maturation of tissues (Calabrese and Sorenson 1977), growth retardation and functional deficits, including central nervous system injury or retarded development, usually result from insult during this stage of development. The developing brain and central nervous system are particularly susceptible to impact, since development processes, including myelination, are not complete, even at birth. Further, the developing fetus is likely to be more susceptible to insult by toxic substances because of the incomplete development of its liver enzyme systems, and a relatively poorly developed blood–brain barrier (Calabrese and Sorenson 1977).

TABLE 29

EFFECTS OF CHEMICAL EXPOSURE DURING HUMAN DEVELOPMENTAL PERIODS ASSOCIATED WITH INTRAUTERINE LIFE

Functional Period	Intrauterine Time Period	Developmental Stage	Developmental Decrement
Fertilization and Implantation	Conception – 17 days	Primary germ cells; blastocyst; gastrula	Cell death – alternative cells recover and multiply; organism death with abortion or reabsorption
Embryonic Development	18–55 days	Organogenesis	Morphologic or organ system abnormalities
Fetal Development	56 days – Term	Growth; maturation of tissues; several differentiations	Growth retardation; functional deficits

Source: Developed from the data of Kurzel and Cetrulo (1981).

A variety of toxic compounds are capable of being transplacentally transmitted from human mother to fetus, and an even larger array of substances can be transferred from mother to newborn in breast milk. Among those substances transferred transplacentally are cadmium (Korpela et al. 1986; Bonithon-Kopp et al. 1986; Lauwerys 1986), lead (Korpela et al. 1986; Bonithon-Kopp et al. 1986; Li 1988), mercury (Bonithon-Kopp et al. 1986; Harada 1977; Takeuchi 1972; Spencer et al. 1988), hexachlorobenzene (Bush et al. 1984), metabolites of DDT (Rogan et al. 1986b), dieldrin (Colborn 1989), and polychlorinated biphenyl (PCB) (Rogan et al. 1988; Rogan et al. 1986b; Bush et al. 1984; Jacobson et al. 1983; Kodama and Ota 1980; Masuda et al. 1978; Polishuk et al. 1977; Funatsu et al. 1972). Among the contaminants potentially transferred from mother to infant in breast milk are cadmium (Dabeka et al. 1986; Sternowsky and Wessolowski 1985), lead (Sternowsky and Wessolowski 1985), mercury (Colborn 1989), hexachlorobenzene (Mes et al. 1984; Mes and Davies 1979), metabolites of DDT (Rogan et al. 1987; Davies and Mes 1987; Rogan et al. 1986a; Mes et al. 1986; Mes et al. 1984; Cone et al. 1983; Mes and Davies 1979), dieldrin (Davies and Mes 1987; Mes et al. 1986; Mes et al. 1984; Mes and Davies 1979), hexachlorocyclohexane (Davies and Mes 1987; Mes et al. 1986; Mes et al. 1984; Mes and Davies 1979), heptachlor epoxide (Mes et al. 1986; Mes et al. 1984; Mes and Davies 1979), chlordane fractions, including oxychlordane and trans-nonachlor (Davies and Mes 1987; Mes et al. 1984; Mes and Davies 1979), photomirex (Davies and Mes 1987; Mes et al. 1986), and polychlorinated biphenyls (Rogan et al. 1987; Mes et al. 1987; Rogan et al. 1986a, b; Mes et al. 1986; Mes et al. 1984; Cone et al. 1983; Wickizer et al. 1981; Mes and Davies 1979; Grant et al. 1976).

The concept of transgenerational effects resulting from exposure to an exogenous chemical compound is not new. Traditional teratology has frequently associated morphologic alterations and physical malformations in the embryo or fetus with the impacts of *in utero* exposure to external dismissal agents. Classic examples are to be found in association with known administration of prescription drugs, e.g., limb deformities associated with maternal dosages of thalidomide during pregnancy (Tuchmann-Duplessis 1975), and genital anomalies associated with maternal ingestion of diethylstilbestrol (DES) to prevent miscarriages (Kurzel and Cetrulo 1981). Additional evidence is provided from a considerable body of knowledge developed from research on the use of "recreational drugs", e.g., craniofacial anomalies associated with fetal alcohol syndrome (Able 1984; Jones et al. 1973), and reduced head circumference and body size of infants who were exposed to nicotine as a result of maternal smoking (USPHS 1979).

Only recently, however, have investigations been oriented toward the more subtle transgenerational effects of exogenous chemical substances. Some of these studies have been oriented toward chemical substances to which the mother was deliberately exposed, e.g., alcohol (Coles et al. 1985; Golden et al. 1982; Streissguth et al. 1980, 1983, 1984), marijuana (Fried 1982), cocaine (Chasnoff et al. 1985), and methadone (Hans et al. 1984). Other studies considered the effects of inadvertent maternal exposures, chiefly to environmental contaminants, e.g., lead (Bellinger et al. 1987; Ernhart et al. 1987; Dietrich et al. 1986), mercury (Harada 1976; Takeuchi 1972a, b), and polychlorinated biphenyls (Jacobson et al. 1985; Rogan et al. 1986a).

From these studies of subtle effects resulting from transgenerational exposures to exogenous chemical substances, i.e., effects other than physical dysmorphology, a series of principles have emerged. These include:

1. Transgenerational effects are negative, frequently subtle, and diminish the potential of the impacted offspring, either physically, behaviorally, emotionally, cognitively or in some combination of these factors, (Rogan et al. 1988, 1986a, 1986b; Jacobson et al. 1990a, b, 1985, 1984a).

2. Exposure to exogenous chemical substances which may produce asymptomatic, sub-clinical, or no apparent effects in the pregnant mother, may have profound effects upon the embryo or fetus (Takeuchi 1972b; Jacobson et al. 1985; Rogan et al. 1986a; Rogan et al. 1988).

3. If maternal effects are observed as a result of exposure, the sequelae observed in infants born to these mothers may differ significantly both in character and degree (Takeuchi 1972a; Funatsu and Yamashita 1972).

4. The deficits produced in transgenerationally exposed offspring are usually durable, i.e., of a long-lasting nature, frequently persisting a life-time (Jacobson et al. 1990a, b; Rogan et al. 1988; Harada 1977; Takeuchi 1972b).

5. Transgenerational exposure may result in clinically normal newborns whose long-term deficits are not evident until later in life (Jacobson et al. 1990; Jacobson et al. 1989).

6. Not only is the extent and duration of exposure important to the degree or magnitude of the effect observed, but the timing of the exposure is critical to the character and potential of the adverse outcome (Kurzel and Cetrulo 1981; Jacobson et al. 1989; Jacobson et al. 1990; Harada 1976).

7. Profound transgenerational effects may result from either an acute, single maternal exposure (Rogan et al. 1988; Rogan 1982; Wong and Huang 1981; Harada 1976; Higuchi 1976), or, because of the excessive biological half-lives of some of these compounds (Bush et al. 1984), transgenerational effects may result from small, cumulative exposures over an extended period of time (Jacobson et al. 1990a, b, 1984a, b; Rogan et al. 1986a, b).

8. Because of the excessive biological half-lives of some of these compounds and their storage in maternal tissues, transgenerational effects in progeny may occur in association with pregnancies occurring years after maternal exposure has ceased (Harada 1976; Abe et al. 1975).

9. Because of the extensive biological half-lives of some of these compounds, there is a potential for multi-generational effects, i.e., a single maternal exposure may effect more than one generation of the progeny born to that mother (Swain 1988).

Now, as never before, the developing body of knowledge related to transgenerational effects has underscored the need to evaluate the safety of chemicals never intended for human consumption.

2.2.6 Case Studies of Multiple Effects of Compounds of Concern

2.2.6.1 Adverse Consequences of Eutrophication in Estuaries And Coastal Seas

Although nitrogen and phosphorus are essential for plant growth, excesses of these nutrients produce severely negative impacts on aquatic and marine ecosystems. Among these deleterious effects are hypoxia, anoxia, reduction of plant biomass, and the proliferation of nuisance algae blooms. These negative consequences of eutrophication are discussed in the following case study.

Anoxia And Hypoxia

Anoxia is the complete removal of dissolved oxygen from the water column, an event which obviously causes widespread damage to aquatic plants and animals. Even mobile animals which can escape from anoxic waters can suffer population declines from the loss of habitat area. For example, in parts of the Baltic Sea cod eggs laid in oxic surface waters sink into anoxic bottom waters where they die (Rosenberg et al. 1990). Oxygen concentrations in the bottom waters of the deep basins of the Baltic between 1969 and 1983 are correlated with codfish populations (Hansson and Rudstam 1990). Price et al. (1985) have speculated that the decline of striped bass populations in part of Chesapeake Bay may be a result of the increasing volume of anoxic bottom waters; the striped bass have been forced into more shallow and warmer waters, waters which may in fact be excessively warm for this species to thrive.

Oxygen need not be completely absent for damage to occur, and a lowering of oxygen to concentrations as low as 3 to 4.3 mg liter^{-1} can cause ecological harm in some estuaries and coastal seas (EPA 1991). Such a depletion of oxygen is termed hypoxia. Examples of ecological damage from hypoxia include lowered survival of larval fish, mortality of some species of benthic invertebrates, and loss of habitat for some mobile species of fish and shellfish which require higher concentrations of oxygen, such as lobster and codfish (Baden et al. 1990; EPA 1991). Significant mortalities of lobsters and population declines of both lobster and codfish have been observed in some Swedish coastal waters as a result of increased incidences of hypoxia (Baden et al. 1990).

Anoxia and hypoxia are major and growing problems in many estuaries and coastal seas. Over the past few decades, the volume of anoxic bottom waters has been increasing in Chesapeake Bay (Officer et al. 1984; D'Elia 1987), the Baltic Sea (Larsson et al. 1985), and the Black Sea (Lein and Ivanov 1992). The apex of the New York Bight (an area of some 1,250 km^2) becomes hypoxic every year, and a large region of the Bight became anoxic in 1976 (Mearns et al. 1982). Hypoxic events appear to be becoming more common in waters such as Long Island Sound (EPA 1991; Parker and O'Reilly 1991), the North Sea (Rosenberg 1985), and the Kattegat (the waters between Denmark and Sweden; Baden et al. 1990), although historical data on oxygen concentrations in coastal waters are often poor.

Anoxia and hypoxia result from oxygen consumption exceeding oxygen supply. Oxygen is supplied to waters through the process of photosynthesis and through diffusion from the atmosphere. Oxygen is consumed by the respiration of organisms, including animals, plants, and the decomposing activity of microorganisms. Eutrophication greatly increases the chances of anoxia and hypoxia by increasing the rate of respiration (Officer et al. 1984; Larsson et al. 1985; Jensen et al. 1990; Rydberg et al. 1990; EPA 1991; Parker and O'Reilly 1991; Lein and Ivanov 1992). Photosynthesis by phytoplankton produces oxygen, but much of the photosynthesis in eutrophic waters occurs near the surface, and oxygen readily diffuses to the atmosphere. The majority of the phytoplankton material is decomposed deeper in the water column, consuming oxygen there.

Many estuaries and coastal seas are stratified due to density differences resulting from freshwater running out over denser seawater. Such stratification increases the likelihood of anoxia and hypoxia, since particulate organic matter sinks into the deeper water but oxygen must mix down through the pycnocline. However, even in the absence of stratification, eutrophication can lead to anoxia and hypoxia, as indicated by nutrient enrichment experiment at the Marine Ecosystem Research Laboratory (MERL) facility at the University of Rhode Island. MERL consists of a series of mesocosms, large fiberglass tanks containing water and bottom sediments from Narragansett Bay, designed to mimic the functioning of estuarine ecosystems. In a nutrient enrichment experiment in which the tanks were kept well mixed, moderate nutrient inputs caused hypoxia, and anoxia resulted from high nutrient inputs (Oviatt et al. 1986).

Dieback of Seagrasses and Algal Beds

In addition to anoxia and hypoxia, eutrophication can lead to the die-back of seagrass beds, important habitat and nursery grounds for a variety of fish and other animals. One mechanism for such die-back is shading out of the grasses by the abundant phytoplankton in the overlying water, a process thought to have caused the die-back of macrophytes in the upper portions of Chesapeake Bay (Kemp et al. 1983; Twilley et al. 1985; D'Elia 1987); in the Dutch Wadden Sea (Gieson et al. 1990), and of both tropical and temperate seagrasses in Australia (Kirkman 1976; Cambridge and McComb 1984; Cambridge et al. 1986). Die-back caused by such shading usually manifests itself in a rather gradual loss of the seagrasses (Robblee et al. 1991), although the occurrence of unusual nuisance algal blooms in 1985 and 1986 greatly reduced the abundance of seagrass beds near Long Island (Dennison et al. 1989). Nitrogen

enrichment may also have a direct physiological response on seagrasses, with internal nutrient imbalances appearing to lead to reduced survival (Burkholder et al. 1992b).

Beds of attached macro-algae on bottom sediments or rocks can also be adversely affected by eutrophication. Nutrient enrichment of rocky intertidal areas typically leads to a reduction in the overall diversity of both attached algae (Borowitzka 1972; Littler and Murray 1978) and associated animals (Gappa et al. 1990). These nutrient-enriched areas tend to be dominated by opportunistic algae with rapid growth rates, such as *Cladophora* sp. and *Enteromorpha* sp. which can take advantage of the elevated nutrient levels and shade out other species (Littler and Murray 1975, 1978). This is clearly seen along the Swedish coast of the Baltic Sea, where, since the mid-1970's, nuisance forms of filamentous algae (*Cladophora* and *Enteromorpha* species) have become more dominant, coinciding with a decline of the former dominant bladderwrack algae, *Fucus* sp. (Baden et al. 1990; Rosenberg et al. 1990). The bladderwrack is used as spawning grounds for herring, and the change in dominance by macroalgae has led to decreased hatching of herring eggs (Rosenberg et al. 1990).

Nuisance Algal Blooms

Blooms of nuisance algae are characterized by very high abundances in the phytoplankton of one overwhelmingly dominant species. These blooms often result in noticeable color and are popularly named by this color: red tides, green tides, brown tides. As with eutrophication generally, these blooms can result in anoxic or hypoxic conditions. In addition many nuisance blooms produce substances toxic to aquatic organisms or humans (Cosper 1991). Green tides during the 1950's heavily damaged oyster populations on Long Island (Ryther 1954, 1989), and brown tides in 1985 and 1986 greatly reduced populations of bay scallops on Long Island (Cosper et al. 1987; Bricelj and Kuenstner 1989) and of blue mussels in Narragansett Bay (Tracey et al. 1989). These shellfish starved to death, since they were unable to graze on the brown-tide algae. Blooms of some dinoflagellates (red tides) can result in the accumulation of toxins in shellfish, which, when eaten by humans, cause paralytic or diarrhetic shellfish poisoning (Smayda 1989). Frequent blooms of a gold-brown dinoflagellate in Northern Europe have caused extensive fish mortality since the mid 1960's (Smayda 1989). In 1991, toxins produced by a diatom bloom concentrated in anchovy and caused the death of pelicans which fed on these fish (Work et al. in press, as cited in Smayda 1992). Production of toxins by diatoms was completely unknown before 1987 (Smayda 1992). Recently, Burkholder et al. (1992a) discovered a new toxic dinoflagellate which releases toxins only in the presence of fish and appears to be responsible for several fish kills in estuaries in North Carolina.

Nuisance-bloom tides have been known since biblical times (Cosper 1991), but blooms of many species appear to be occurring with greater frequency throughout the world (Hallegraeff et al. 1988; Anderson 1989; Smayda 1989, 1992; Robineau et al. 1991). Red-tide blooms of toxic dinoflagellates appear to be more frequent in many parts of the world (Anderson 1989; Smayda 1989; Wells et al.. 1991), and blooms of cyanobacteria have become more prevalent in the less saline portions of Chesapeake Bay (D'Elia 1987) and in the Baltic Sea and related waters over the past 10 to 20 years (Smayda 1989 and references therein). Many of the new toxic

phytoplankton blooms are sub-populations of previously non-toxic species which now occur at previously unseen abundances (Smayda 1989, 1992). Brown-tide blooms of *Aureococcus anophagefferens* were unknown before 1985 (Sieburth et al. 1988).

The cause(s) of increased nuisance blooms is/are not known, but evidence points toward the importance of increased nutrient inputs to estuaries and coastal seas. Smayda (1989) has compiled extensive evidence in support of the hypothesis that the worldwide increase in nuisance algal blooms is related to increased nutrient availability. For instance, a 2.5-fold increase in nutrient loadings accompanied an 8-fold increase in the annual number of red-tide blooms in a harbor in Hong Kong between 1976 and 1986. Increased nutrient concentrations in the North Sea, the Baltic Sea, and in waters between Denmark and Sweden (the Skagerrak and Kattegat) have co-occurred with increased primary production and increased incidence of blooms in these waters (Smayda 1989). The green-tides which occurred in the Great South Bay of Long Island in the 1950's were also clearly associated with nitrogen loading from duck farms there (Ryther 1954), and the reduction of nutrient loadings and opening of a channel to increase water exchange between the bay and ocean have greatly reduced these blooms (Ryther 1989). Also, nuisance algal blooms are much more likely to occur in nutrient-rich estuarine waters than in more coastal or shelf waters (Cosper 1991; Prego 1992).

On the other hand, there is little if any evidence to show a direct connection between either nitrogen or phosphorus concentrations and blooms of most brown-tide or red-tide organisms (Cosper 1991; Wells et al. 1991). Red-tide blooms in Florida are not correlated with concentrations of any measured form of nitrogen or phosphorus (Rounsefell and Dragovich 1966). Similarly, the brown-tide blooms of the mid-1980's along the northeastern coast of the U.S. did not appear to be correlated with higher levels of nitrogen or phosphorus (Cosper et al. 1989; Cosper 1991). However, it is important to note that the concentration of a nutrient at any given point of time may not be correlated with its availability to phytoplankton (Howarth 1988), and phytoplankton can grow for long periods of time off of internally stored pools of nutrients (Andersen et al. 1991).

Perhaps more importantly, it may not be the availability of nitrogen alone that matters in controlling nuisance algal blooms, but rather the relative availability of nitrogen in comparison to silicon (Officer and Ryther 1980; Smayda 1989). When Si:N ratios are relatively high, silicon is relatively available, favoring the growth of diatoms, which have a high requirement for silicon. However, as the Si:N ratio decreases, competition begins to favor other algae with no silicon requirement, such as the red-tide, green-tide, and brown-tide organisms. Eutrophication can decrease the abundance of silicon by increasing sedimentation of phytoplankton, as has been demonstrated in the Baltic Sea (Wulff et al. 1990). Where long-term nutrient data are available, the increased occurrence of nuisance algal blooms has always been found to be correlated with a decrease in Si:N ratios (Smayda 1989 and references therein). Net primary production probably remains controlled by nitrogen or phosphorus availability throughout the range of silicon availabilities (Howarth 1988), but the relative availability of silicon may well control the abundance of diatoms vs. other phytoplankton species, thereby setting the stage for nuisance blooms (Smayda 1989).

2.2.6.2 Multiple Effects of a Single Class of Contaminants, PCDDs

Not only do the compounds of concern, as a group, generate all of the effects discussed above, but an individual compound or class of compounds may do so as well. This section discusses the multiple effects of 2,3,7,8–tetrachlorodibenzo–*p*–dioxin (TCDD), considered to be the most toxic of 75 congeners, or isomorphic shapes, that compose the class of contaminants polychlorinated dibenzo–*p*–dioxins (PCDDs). TCDD was the primary source of public health concern at Love Canal, New York; Seveso, Italy; and Times Beach, Missouri. In different species, and in different tissues within a species, TCDD is known to cause cancer, impair the immune system, initiate wasting syndrome, adversely affect the nervous system and behavioral patterns of individuals, disrupt the endocrine system, and elicit embryo– and fetoxicity, as well as other reproductive effects, and for laboratory rats and chimpanzees, have transgenerational effects. That TCDD is responsible for this "perplexing web of interaction" has been explained by two mechanisms: one which spurs some cell types to grow wildly, and another which inhibits or causes deviations in some cell types as they differentiate to their respective specialized functions (Schmidt 1992). Consequently, TCDD has recently been characterized as an "environmental hormone", because it can alter the functional activity or the structure of various organs in numerous species. This case study will focus on known human health effects and implications of the results from laboratory and wildlife population studies.

TCDD is presently considered less of a human cancer risk than was once believed. However, two recent epidemiological studies support the hypothesis that, at least at relatively high doses, TCDD can be a human carcinogen. Fingerhut et al. (1991) found that 5,172 workers from a dozen chemical plants at which exposure occurred had a 15 percent increased chance of dying from cancer, in comparison to the general population. These findings were based upon blood serum concentrations of TCDD in 259 of these workers.

Workers with twenty or more years exposure, (including a period in which TCDD exposure levels would have been higher) exhibited a nine–fold increase in soft–tissue sarcomas as compared with the general population. Similarly, researchers found a 24 percent higher rate of death from all cancers in 1,583 pesticide plant workers in Germany, and a 87 percent increase for a twenty year exposure group (Manz et al. 1991). Unlike the U.S. study, the German study did not find an association with any single form of cancer. A critical review of the literature concluded that because of the array of compounds (including pesticides) also present during any occupational exposure to TCDD, particularly spraying or other application jobs, it is not yet possible to assign a causative effect to TCDD alone for malignant lymphomas, and possibly not for soft–tissue sarcomas (Johnson 1992). This author did find that respiratory system and thyroid cancers occured at an excessive rate suggestive of a causative role for TCDD.

Both the humoral–mediated immune response, e.g., antibody reactions, and the cell–mediated immune response, e.g., lymphocyte rejection of foreign tissues or tumors, are affected in most species (WHO 1989). Recent research (House et al. 1990) has indicated that there is "a profound suppression of antibody production" in mice exposed to TCDD which occurs in a dose–dependent fashion, with a significance level less than 0.01. These findings support the results

from earlier research (Vecchi et al. 1980; Holsapple et al. 1984). In addition, these authors suggest that TCDD selectively induces toxicity at the cellular level, thus allowing for multiple assaults on the host's immune functions. The thymus, and particularly its epithelial cells, are sensitive to TCDD exposure, as indicated by the occurrence of lesions at levels well below those inducing lesions in other organs in studies conducted on rats, mice, guinea pigs, and monkeys. Interestingly, the effect of TCDD on lymphoid tissues is the same in all species and exerts its most profound and persistent effects when introduced during the perinatal period (WHO 1989). Nonetheless, researchers have not found consistent results implicating immunosuppression in accidentally exposed humans (Hoffman et al. 1986); however, their offspring have not been investigated.

TCDD has been found to cause a starvation-like wasting syndrome in all animal species subjected to acute lethal doses (EPA 1985; Bestervilt et al. 1991). Early studies suggested that food consumption was decreased, but the reduction of intake could not fully account for the weight loss (Allen et al. 1975, 1977; Greig et al. 1973; Kociba et al. 1976). Subsequent studies directed toward the digestive tract could not elicit a generalized impairment of intestinal absorption (Madge 1977; Manis and Kim 1979; Ball and Chabra 1981; Shoaf and Schiller 1981; Schiller et al. 1982). Keesey et al. (1976) suggested that body weight in rats is regulated around an internal setpoint, which is lowered by TCDD. These and other authors found that TCDD-treated rats vigorously maintained the new, lower setpoint, whether starved or overfed, with the same precision as the control group (Keesey et al. 1976; Peterson et al. 1984). Wasting syndrome has been listed as a symptom, although not necessarily confirmed as an effect, of human exposure to TCDD (ATSDR 1989).

There are a variety of human neurological and behavioral impairments that have been associated with acute exposure to TCDD or mixtures containing TCDD, including sexual dysfunction (lack of libido and impotence); headache; abnormal nerve conduction and clinically uncorroborated joint pains; sleep disturbance; depression; loss of energy and drive; uncharacteristic bouts of anger; and possibly sight disturbance and loss of hearing, taste, and smell (Fillipini et al. 1981; WHO 1987). There have been only two cases of exposure to "pure" TCDD, which involved a total of seven people. The exposed class, as a whole or individually, exhibited all of the above symptoms, sometimes for up to two years after exposure. There were also individual instances of hirsutism, chloracne, and other effects indicating alterations in body chemistry. It was considered likely, but not conclusive, that the delayed manifestation of these symptoms was due to the original TCDD exposure.

Human health effects at the individual and population level from chronic exposure to TCDD have not been identified. However, a critical need in future research can be identified by examining the results from experimental studies and research on wildlife populations with regard to behavioral impairments, endocrine system alterations, reproductive and developmental toxicity, and transgenerational effects.

A subtle form of behavioral impairment has been identified in a multigenerational experiment involving non-human primates. Schantz and Bowman (1989) found a dose-

dependent relationship in the offspring of female rhesus monkeys which were fed daily diets containing 0 ppt, 5 ppt, and 25 ppt of TCDD. Several years after secondary offspring exposure (*in utero* and four months of nursing) had ceased, these authors found a dose-dependent relationship for spatial discrimination reversal learning (DRL) and suggested a NOAEL of 5 ppt. Bowman et al. (1989) expressed concern that this may be an artificial NOAEL because the TCDD lipid values were assumed to be zero for the offspring of the controls, which actually may have background concentrations of TCDD-like substances, such as furans and PCBs, that could elicit the same effects, and because individuals varied greatly in their abilities to metabolize the dose received from the mother. Similar infant exposures to PCBs have been correlated with subtle cognitive impairments (Rogan et al. 1988; Swain 1988; Jacobson et al. 1990; Tilson et al. 1990; Jacobson et al. 1992). The ultimate impact of these individual cognitive impairments can be characterized as a "diminishment of potential" in humans.

Endocrine disruption, reproductive and developmental effects, and transgenerational effects have distinct profiles resulting from acute doses, but the distinctions blur somewhat when considering lesser exposures. TCDD exerts antiestrogenic, estrogenic, and antiandrogenic effects on the endocrine system resulting in inter alia, decreased uterine weight, estrogen-induced protein secretion, and estrogen and progesterone receptors; and decreased androgen secretion, reduced testosterone levels by 90 percent, testicular atrophy, reduced fertility, and decreased spermatogenesis (See Effects on Reproduction). Reproductive effects include morphological changes in the ovaries and uterus of rats (Kociba et al. 1976), reduced conception rates and a high incidence of early spontaneous abortions in monkeys (Allen et al. 1977; Barsotti et al. 1979). Peterson et al. (1992) have found an ED_{50} of 0.16 ppb in rats, based on a single maternal dose on Day 15 of gestation. Peterson found indications of demasculinization at the lowest dose administered, 0.064 µg/kg body (64 ppt). He has not determined a NOAEL. This dosage was transferred to the pups *in utero* and through lactation, to be associated with a range of adverse effects in the development of the male reproductive system and in behavior, including delayed and incomplete organ development, inhibition of spermatogenesis, both demasculinization and feminization of sexual behavior, and alteration of the regulation of the luteinizing hormone. Lowered sperm production of 75 percent did not affect the rats' fertility. Normally, rats ejaculate up to ten times the amount of sperm needed to ensure pregnancy.

Developmental toxicity can be described in terms of embryo/fetotoxicity, structural malformations, and postnatal functional alterations (USEPA Draft 1991). Except for the hamster, the lethal effect of TCDD on the fetus is likely secondary to maternal toxicity, i.e., the fetus dies only when there are apparent adverse effects on the mother from the dose. Structural malformations include thymic hypoplasia, hematological alterations, subcutaneous edema, extra ribs (rabbit), cleft palate malformation (mouse), and intestinal hemorrhage (rat). There have been two studies focusing solely on the transgenerational effects of TCDD. One involves the effects of exposure on the reproductive system and behavior of rats (Murray et al. 1979), and the other on the reproductivity and behavioral effects on rhesus monkeys (Bowman et al. 1989). Murray et al. (1979) conducted a three generation reproductive study on Sprague-Dawley rats fed daily diets containing 0, 0.001 ppm, 0.01 ppm, or 0.1 ppm TCDD. The groups in the first generation were fed for 90 days prior to mating. No effect on mating frequency was observed, nor were

any toxic effects. However, the offspring and third generation that were then also fed a diet containing 0.01 ppm TCDD per day showed decreased body weight and reduced food consumption. The first generation's fertility was greatly reduced at a dosage of 0.01 ppm per day, and the second and third generations' fertility levels were significantly reduced at dosages of 0.001 and 0.01 ppm per day, respectively. The 0.01 ppm dosage also resulted in reduced litter sizes, an increase in feto- and neonatal mortality, and a decrease in postnatal growth. As a result, 0.001 ppm per day TCDD was suggested as a NOAEL for reproductive lesions. However, reevaluation of the same data from a transgenerational perspective (all generations statistically pooled) indicated that 0.001 ppm did have a statistically significant effect, and thus should not be used as a NOAEL (Nisbet and Paxton 1982). This level of effect is supported by additional reevaluation of these data by Allen et al. (1989) and by data from the rhesus monkey study (Schantz et al. 1989).

The potential human health impact of TCDD exposure based on the sum of known endocrine, reproductive, and transgenerational effects in experimental and wildlife populations includes: (1) TCDD has an extended half-life and can thus keep a gene "on" or "off" for an excessive amount of time, or be transferred *in utero* or through lactation to the next generation in sufficient amounts to cause harm. Because of this extended biological half-life and the apparent absence of a threshold for adverse effects, the reproductive system appears to be the most sensitive to TCDD exposure, particularly during the perinatal period; (2) there is existing evidence which suggests that prenatal androgenization affects human sexual behavior and structure of the hypothalamus (Erhardt and Meyer-Bahlburg 1981; Hines 1982; LeVay 1991), thus altering the nature of human reproductivity; and (3) unlike rats who ejaculate 10 times more sperm than needed for successful fertilization, humans have almost no margin for error in terms of successful insemination (Carlsen et al. 1992). Consequently, impairment of spermatogenesis would likely have a negative impact on human fertility (Peterson et al. 1992). Thus, it is possible, but not yet demonstrated, that the cumulative impact of chronic and *in utero* exposures humans receive have been and/or are affecting both the nature and success of human reproductivity at the population level.

2.2.6.3 Effects Of Multiple Compounds of Concern On a Single Species: Forster's Tern

A case study of the Great Lakes Forster's tern provides an example of the difficulty in recognizing subtle effects and sensitive endpoints resulting from ambient exposure to multiple chemicals over time. Overt endpoints of high-dose exposure, such as birth defects and outright mortality, are far easier to observe than low-dose functional deficits that are not expressed immediately after birth. Consequently, as conditions of the environment improve and exposure levels decrease, less visible, widespread health decrements in wildlife and human populations could be missed as the following case study demonstrates.

A cross-disciplinary team of researchers observed a colony of troubled Forster's terns (*Sterna forsteri*) in Green Bay in 1983 and 1988 (Hoffman et al. 1987; Kubiak et al. 1989). The

study population was a colony of nesting Forster's terns on a confined waste disposal facility in Green Bay, Lake Michigan, Wisconsin. The tern control population was nesting on an inland lake and not dependent upon food sources from the Great Lakes. Nesting success was recorded and samples of eggs and chicks were collected for chemical and *in vitro* analysis of bioaccumulative contaminants. In 1983, tern offspring experienced significantly poor hatchability (37 percent compared with controls at 75 percent), low chick body weight, increased ratio of liver to body weight, edema, reduced fledgling success, and lack of parental care compared with the in-land population (Kubiak et al. 1989). Seventeen days after hatching, 35 percent of the chicks had died. In one component of this study, an egg exchange experiment among the Green Bay colony, the control colony, and laboratory incubators revealed that embryotoxicity, chick mortality, and parental abandonment contributed to the lack of nesting success of the Green Bay terns.

Significantly higher concentrations of PCBs and dioxins were found in the Green Bay colony. Tissue culture bioassay for AHH enzyme induction revealed significantly higher enzyme activity measured as dioxin toxicity equivalents (TEQs) in the Green Bay population than controls. Going one step further, this was confirmed using PCB congener-specific chemical analysis and multiplying AHH enzyme induction toxicity factors by the quantities of specific congeners in chicks and abandoned eggs. The congener-specific chemical determination revealed that 95 percent of the toxicity was from PCBs and about 3 percent from dioxins.

The scenario at the Green Bay colony changed considerably in 1988 (Harris 1990) although the final outcome was similar. The median total PCBs in the eggs in 1983 was 22.2 ppm. In 1988, the eggs held 7.3 ppm (median), a 66 percent reduction. Dioxin enzyme induction toxicity equivalents declined 58 percent, from 2175 to 913 (201 enzyme-induction TEQs in the referent population). Certain endpoints — hatchability, length of incubation, weight gain, and number of young fledged — were normal and did not deviate significantly from the 1983 control population up to 17 days posthatching. However, in the latter quarter of development, commencing on day 18, the chicks showed signs of wasting and by day 31, 35 percent of the young had died. This was the same proportion that had died in 1988, but two weeks later. Thus far, wasting appears to be the most sensitive endpoint researchers have identified in Forster's terns as a result of exposure to dioxin-like contaminants. If the higher-dose endpoint of hatchability, an obvious and easy endpoint to measure, had been used as the only endpoint of the second study, the delayed, but equally devastating effect of wasting would have been missed.

Other latent effects in the Forster's terns were not reported because the short-term and long-term fate of the chicks that fledged was not determined beyond day 31. Long-term banding and breeding population assessments have not been conducted to determine if this population of Forster's tern existed because of immigration of breeding birds from clean areas as is the case with Great Lakes bald eagles (*Haliaetus leucocephalus*) and Caspian terns (*Hydroprogne caspia*) (Colborn 1991, L'Arrivee and Blokpoel 1988).

Two facts are worth noting: (1) no Forster's terns have returned to the Green Bay Island since 1988 (Ludwig 1992); and (2) no lesion for wasting has ever been identified. A laboratory study in which 2,3,7,8-TCDD was administered to rats intracerebroventricularly into the lateral brain ventrical and subcutaneously at the back of the neck at a pumping rate of 1 µl/h or 20-21 µg/kg body weight per day induced wasting only in the brain treated animals, suggesting that wasting may be the result of central nervous system damage (Pohjanvirta et al. 1989).

2.2.7 Conclusion

Atmospherically transported toxic contaminants impacting the world's great waters represents one of the largest challenges facing the scientific and managerial communities today. The problems associated with identifying and ultimately managing the sources, fate, transport, effects, control, and remediation of toxic contaminants in large marine and aquatic ecosystems are among the most difficult contemporary issues confronting environmental managers and decision-makers.

While loadings and inputs of toxic chemicals are direct, variable, and waterbody specific, it is clear that all of the world's great waters are being perturbed by contributions of toxic substances from the atmosphere. In most cases, the sources driving the atmospheric concentrations are poorly understood, and the dimensions of the airsheds for each of the world's great waters are largely unknown. An increasing body of evidence indicates that long-range transport of atmospheric contaminants results in transboundary pollution of the world's great waters, and that this mechanism does not respect geographical, political, jurisdictional, or national boundaries.

The fate of toxic substances in large marine or aquatic ecosystems is presently incompletely understood, but it is recognized as critically important because of the uptake of contaminants by native biota. Within the waterbody, the phenomenon of biomagnification often results in excessive increases in contaminant concentration at each succeeding trophic level in the food chain. Food chain accumulation ultimately leads to human exposure, as humans are one of the final predators in the great waters ecosystems.

The data presented in this report repeatedly demonstrate that all of the ecosystem compartments of the world's great waters -- i.e., the atmosphere, the water column, the sediments, and the biota, including humans -- are irrevocably interrelated, interconnected, and reciprocally interactive. They further indicate that by the time the sources, fate, transport, and effects of a toxic compound are identified and understood, it is too late, and the inevitable impacts of those materials on the system will have occurred. Therefore, in addition to remediating past inputs, a philosophy of prevention is mandated. In order to respond to this challenge, the regulatory community will be required to implement a prevention policy which is guided by a perspective of our interrelated environment, and which extends beyond both environmental compartments, and local, state, provincial, regional, national, and international boundaries.

Overview of the Current State of the Great Waters.

As a result of our increased understanding of the effects of nutrient additions and the implementation of control practices, eutrophication is beginning to be managed in many of the world's great waters. For a number of these systems, water clarity has improved and anoxia has been minimized. While significant improvement has been made for many of the great waters in the last two decades, some areas still require additional efforts.

Toxic residues in some of the ecosystem compartments of many of the world's great waters have begun to decline. However, the observed rates of decline have recently decreased, and, in many areas, it is considered inadvisable to consume the biota of these waters. In many of these systems, obligate fish consuming wildlife are adversely impacted, and frequently fish stocking is required because of reproductive failures in the fish populations. In many areas, fish consumption advisories are in effect as a part of an effort to minimize or eliminate negative impacts of toxic chemicals on human health. The slow response times of many of these bodies of water suggest that extended periods of time, on the order of decades, will be required before these systems recover completely from past and present chemical insult, even when all sources of toxic substances are eliminated.

In summary, for most of the great waters, present conditions are significantly improved as compared with two to three decades ago. However, the majority, if not all, of these systems are far from fully recovered.

Chemical Contaminant Profile Summaries.

This section summarizes the present state of knowledge and the current status for a number of compounds known to be atmospherically transported to the world's great waters. Each major chemical or contaminant class of compounds is considered individually below.

2,3,7,8–Tetrachloro–p–dibenzodioxin.

As long as industrial society continues to depend upon incineration and combustion processes as a source of energy, a means of waste disposal and a process of production, TCDD will be a source of concern. Present concentrations of 2,3,7,8–TCDD in human adipose tissue are globally quite consistent in the 5 to 10 ppt range. However, because the analytical techniques required to measure dioxins have only recently become standardized, there is no present method available to estimate whether body burdens in the human population are increasing or decreasing as compared with historic backgrounds. The non–carcinogenic effects of dioxin have recently received increasing attention, and appear to be as subtle, and possibly more serious, than the potential for cancer. Dioxin is still considered the most toxic xenobiotic substance produced by human activity. While its effects are dramatically different among various species, the greatest exposure pathway in most instances is the ingestion of contaminated foodstuffs. Fetuses and nursing infants are at exceptional risk to exposure, even more so than individuals eating 2,3,7,8–TCDD contaminated fish.

Cadmium

Cadmium exposure is an excellent example illustrating the fact that a relatively constant low-dose exposure from multiple pathways can produce a slow, but steady, increase in the body burden of the contaminant in a population. Worldwide body burdens of cadmium are rapidly approaching the maximum safe tolerance limits. Inhalation of cigarette smoke is the most important exposure pathway, with consumption of contaminated foodstuffs a close second. Gross teratological and behavioral changes have been reported in experimental animals following cadmium exposure. Low birth weight has been associated with cadmium exposure in both animals and humans. Long-term industrial exposure to cadmium has been reported.

Chlordane

Even though production of chlordane for domestic use has ceased in the United States, commercial products containing this pesticide are still available until the stocks are depleted. Chlordane and its metabolites in fish have been associated with areas of urbanization, suggesting its misapplication, possibly against termites. In the Great Lakes, oxychlordane concentrations in fish tissue are regarded as having reached a level of concern.

The principal exposure pathway is generally food. However, both inhalation in homes treated with chlordane, or ingestion of contaminated drinking water could become primary pathways in areas where this pesticide was used or disposed of carelessly. An association between fish consumption and human residues of chlordane metabolites has been reported. Chlordane both induces enzyme production and disrupts endocrine control.

DDT/DDE

Concentrations of DDT in human tissue are decreasing; however, its biodegradation product, DDE, does not appear to be declining. Since DDT is not readily converted to DDE in humans, and human residues are declining, it is assumed that the food pathway is contributing to present body burdens of DDE. Although its use has been banned in Canada and the United States, long-range transport of DDE to the great waters will be a continuing problem. DDE is an enzyme inducer, gap junction intercellular communication blocker, and disrupts endocrine control. Concentrations in maternal breast milk have been associated with hyporeflexia in neonates. Human tissue levels of DDE have been associated with the consumption of fish.

Dieldrin

Although the manufacturing and large number of uses of dieldrin have been banned in the U.S., there does not appear to be a decline in human residue levels to date. Dieldrin accumulates in human tissue with age and is preferentially transferred to the fetus via the placenta and to the newborn in breast milk. This toxic substance is an enzyme inducer, gap junctional intercellular communication blocker, and disrupts endocrine hormone control. Exposure likely results from leaching of residuals from past use and improper disposal.

Hexachlorobenzene (HCB)

Hexachlorobenzene is created unintentionally during the production of pesticides and the combustion of chlorine containing material. As a result, it is ubiquitous in the environment. Tissue residue surveys find that HCB concentrations have not declined since 1975 and suggest that concentrations may be increasing. However, food residues in some highly contaminated areas of the U.S. have shown a decline. HCB is capable of enzyme induction and disruption of endocrine control. Severe, long-lasting health effects have been seen in a cohort of people exposed to high concentrations of HCB after eating HCB-treated seed; 95 percent of all *in utero* infants at the time of the incident died within two years of birth. There were many stillbirths as well. Nursing infants ingest 200 to 300 times the adult intake on a bodyweight basis. Significantly higher concentrations were found in cadavers from Kingston, Ontario when compared with Ottawa, Canada. Similarly elevated concentrations of HCB were found in follicular fluids in persons living near Hamilton Harbor when compared with those from other southern Ontario communities. In the Great Lakes, HCB concentrations in fish and water were reported at a level of concern in 1986.

Lead

Recent efforts in lead research have revealed new subtle health effects not previously recognized. These observed impacts included neurological, immunological, developmental, and reproductive effects. Maternal prenatal exposure has been associated with low birth weight, shortened gestational age, neurobehavioral, and psychomotor deficits in offspring, confirming that lead is a human neuroteratological agent.

Strong associations have been found between lead exposure and detrimental effects on behavior, cognitive, and motor development of infants and children. Because its immunosuppressive actions have been demonstrated in laboratory animals at very low doses, the potential for effects in humans merits serious consideration.

Lindane (Isomer of Hexachlorocyclohexane; HCH)

Isomers of HCH do not appear to be decreasing in human tissues. The alpha isomer of HCH was established to be at a level of concern in the Great Lakes in 1986. The estrogen effects of lindane and its adverse effects upon the male reproductive system have been reported in a variety of animal studies. Because of human breast milk concentrations of this pesticide, nursing infants are at special risk. Lindane induces enzymes, blocks intercellular gap junction communication, and interferes with endocrine control.

Mercury

Human exposure to mercury is associated with both naturally contaminated bodies of water and marine and freshwater ecosystems in which mercury has accumulated as a result of industrial activity. Methyl mercury is of special concern because it is completely absorbed upon

ingestion. Under anaerobic conditions in lake sediments it is converted from metallic mercury to the methyl form and readily bioaccumulates in fish tissue. A number of studies have shown a correlation with human mercury residues and fish consumption. An association with the number of dental fillings of mercury amalgams and mercury residues in blood and urine has been reported. In animals, methyl mercury preferentially crosses the placental barrier and the fetal blood brain barrier, and is neuroteratological.

Polynuclear Aromatic Hydrocarbons (PAHs)

If estimates of continued fossil fuel combustion are realistic, PAHs are going to be a continuing problem for the world's great waters. Improvements in analytical technology have revealed that PAHs bioconcentrate in certain tissues, which was not considered possible in the past because of their rapid enzyme induction capacity. There is no information available to predict the human health effects of PAHs. PAHs tend to accumulate in the sediments associated with great waters, and have been implicated in a variety of tumors and cancers associated with bottom–dwelling fish. Many of the PAHs are potent carcinogens, and some have been shown to be genotoxic agents.

Polychlorinated Biphenyls (PCBs)

Although PCB production has been banned North America, it is estimated that more than 50 percent of total production is still in use. Because of this enormous reservoir, the persistence of this group of compounds, and inadequate disposal methodologies, PCBs will likely continue to be a major problem in the world's great waters. Although pathways contributing to background human exposure have not been clearly defined, a number of studies suggest that inhalation is a minor pathway. Several of the tetra–, penta–, and hexachlorobiphenyls are known inducers of AHH/EROD enzymes, and have been associated with thymic involution, teratogenicity, "wasting", and porphyria in a number of laboratory animals. Some PCB congeners are more toxic than others. These forms induce enzymes, block intercellular communication, and disrupt glucocorticoid control. They have been associated with developmental decrements and reduced birth weights in human infants and with shortened gestation periods. It has been suggested that as PCBs recycle in the world's great waters, the more highly chlorinated (potentially more toxic) congeners will become a larger component of the total PCB concentration in circulation.

Toxaphene

The pesticide toxaphene is a mixture of 177 compounds about which little is known. Its use has been limited. Because of its persistence, biomagnification and dispersal potential via long–range transport, it will continue to be of concern in the world's great waters. In very high doses compared to ambient concentrations, it has been found to be an enzyme inducer, gap junction intercellular communication blocker, and interferes with endocrine control. Toxaphene is listed by USEPA as a Class B2 carcinogen.

2.2.8 Application of New Knowledge Related to Toxic Substances

One of the major needs relative to airborne toxic substances is a methodology which will reliably express the biological toxicity or potency of these compounds. With this tool in hand, a method for quantification of impacts and effects against relative toxicity would be available. This is particularly important when groups of compounds such as polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are considered.

The PCB group of compounds consists of 209 theoretically possible congeners, the PCDD group of substances are comprised of 75 congeners, and the PCDF group of compounds consists of 135 congeners. Each of these congeners are related to the original parent compound, but each differs slightly in degree and position of chlorination, in stereochemistry, and, most importantly, in biological toxicity or potency. The PCB group of compounds probably affords the best example for consideration.

Early toxicological research treated PCBs as a series of commercial mixtures. Normally, results were described as "Total PCBs" or as an Aroclor mixture. In either case, the reference Aroclor was used, ignoring the fact that it consisted of up to 50 or more congeners of PCB, each with varying toxicity. To date, all of the epidemiological studies performed have relied upon the use of "Total PCBs" as a measure of toxicity resulting from exposure. However, there is a growing body of evidence which suggests that only a relatively few highly toxic PCB congeners may be responsible for many of the observed outcomes of exposure (Jacobson et al. 1989; Kubiak 1988; Kannan et al. 1988; Bush et al. 1984 and 1985).

These few highly toxic PCB congeners are generally planar or nearly planar in nature. The planar or nearly planar group of substances include not only non-ortho and mono-ortho substituted PCBs, but also polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs).

Although the various planar congeners of PCBs, PCDFs and PCDDs differ widely in their biological toxicities, they are all quite similar in their stereochemistry and produce similar, characteristic patterns of toxic responses in mammals (Poland and Knutson 1982; Safe 1987; Tillitt et al. 1988a and b). Tillett et al. (1988b) states that it is generally accepted that the toxic properties of various planar chlorinated hydrocarbon compounds are expressed as a function of a common mode of action. Given this fact, it is, therefore, possible to calculate the biological toxicity or potency of any of these compounds either individually or in complex mixtures. This expression of potency is usually made in relationship to the most toxic of the planar chlorinated hydrocarbons, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Ample precedent for this assignment of toxicity as TCDD-equivalents exists (Eadon et al. 1986; Safe 1987; Tillitt et al. 1988a and b; and Kubiak 1988). The usual mechanism employed to evaluate TCDD-equivalent toxicity is to measure the ability of the individual planar chlorinated hydrocarbon to induce mixed function oxidase enzymes in cultures of liver tissue cells. These enzyme assays include aryl

hydrocarbon hydroxylase (AHH) and the cytochrome P-450-dependent ethoxyresorufin-o-deethylase (EROD) in rat hepatoma cell cultures. The magnitude of the enzyme response for an individual planar compound or a complex mixture of these substances is then expressed relative to the magnitude of the response elicited by the most toxic planar compound, 2,3,7,8-tetrachlorodibenzo-p-dioxin, as TCDD-Equivalent Toxicity. The estimation of TCDD Equivalents has been shown to correlate strongly with the observed toxicity in mammals of various individual compounds and mixtures of PCB, PCDF, and PCDD congeners (Sawyer et al. 1984; Mason et al. 1985; and Safe 1987). TCDD equivalents are also variously referred to as dioxin equivalents, toxic equivalencies (TEQs), or toxic equivalency factors (TEFs). Authors will also frequently combine these various designations, e.g., Dioxin-TEFs, TCDD-TEQs.

Kubiak (1988) has prepared a series of conversion factors (Keq) for determining "2,3,7,8-TCDD Equivalents" for compounds isosteric with 2,3,7,8-TCDD, based upon this relative ability of the planar substance to induce aryl hydrocarbon hydroxylase (AHH) and ethoxyresorufin-o-deethylase (EROD). A listing of PCBs and their associated 2,3,7,8-TCDD equivalents is presented in Table 30. In practice, the Keq values are simply multiplied by the concentration of the individual congener to estimate the toxic equivalency (TEQ) or the toxic equivalency factor (TEF) relative to 2,3,7,8-tetrachlorodibenzo-p-dioxin.

The EROD and AHH enzyme induction tests provide separate and independent estimates of the potency or the biological toxicity of a given compound or complex mixture. Under normal circumstances, the values derived from these tests are in good agreement with each other. Since the induced enzyme levels correlate strongly with observed toxicity in mammals, either EROD or AHH results may be reasonably used to estimate the toxicity of those planar chlorinated hydrocarbon compounds whose chief mode of action is enzyme induction. In practical application, a single enzyme induction value is usually derived for either an EROD or AHH induction test for each congener or complex mixture tested. This value is then used to represent the potency of that congener or mixture.

By comparison, TCDD-equivalency values for individual congeners are calculated in the same fashion (Table 30), but direct evaluation of complex mixtures of chlorinated hydrocarbons using TCDD-equivalents must be undertaken with some degree of caution. This is necessary because the calculated TCDD-equivalent value of the sum of the planar compounds will often exceed the value observed upon testing of the mixture by either EROD or AHH protocols. There appear to be two likely reasons that the simple sum of the TCDD equivalent values tend to slightly overestimate the actual enzyme induction observed. While the exact mechanisms are yet unknown, it is known that the toxic interactions between and among the various planar compounds have been shown to exhibit synergism, additivity, or antagonism (Birnbaum et al. 1985; Eadon et al. 1986; Keys et al. 1986; Bannister and Safe 1987). Secondly, it appears that the non-toxic,or relatively non-toxic, non-planar congeners contained in complex mixtures of compounds also tend to compete for the same substrate binding sites as the planar congeners. Since fewer binding sites are available for the more toxic planar structures, proportionately less opportunity exists for induction of enzymes than in the case of a planar constituent measured individually (J. Ludwig, personal communication 1992). The importance of this interaction is apparent when the toxicities of the various Aroclor Standards are compared with the more active enzyme inducers (Table 30).

TABLE 30

CONVERSION FACTORS (KEQ) FOR DETERMINING "2,3,7,8–TCDD EQUIVALENTS" FOR PCB CONGENERS BASED UPON RELATIVE ABILITY TO INDUCE AHH AND EROD ENZYMES

Compound	IUPAC No.	Keq AHH	Keq EROD
2,3,7,8–TCDD	--	1.00	1.00
3,3',4,4',5–PeCB	126	0.40	0.32
3,3',4,4'–TeCB	077	0.0027	0.009
3,3',4,4',5,5'–HxCB	169	0.0016	0.0033
2,3,3',4,4'–PeCB	105	0.0011	0.0006
2,3,3',4,4',5'–HxCB	157	0.000135	0.000063
2,3,4,4',5–PeCB	114	0.000095	0.000142
2,3,3',4,4',5–HxCB	156	0.000046	0.000089
2',3,4,4',5–PeCB	123	0.000024	0.000012
2,2',3,3',4,4',5–HpCB	170	0.000016	0.0000066
3,4,4',5–TeCB	081	0.0000086	0.0000417
2,3,4,4'–TeCB	060	0.0000085	0.0000417
2,3,3',4,4',5,5'–HpCB	189	0.0000085	0.0000102
2,3',4,4',5–PeCB	118	0.0000083	0.0000091
2,3',4,4',5,5'–HxCB	167	0.0000072	0.0000089
2,2',3,4,4',5'–HxCB	138	<0.0000072	<0.0000089
2,3,3',4,4',6–HxCB	158	<0.0000072	<0.0000089
2,2',3,3',4,4'–HxCB	128	<0.0000072	<0.0000089
2,3,4,4',5,6–HxCB	166	<0.0000072	<0.0000089
Aroclor 1232		0.0019394	0.0000019
Aroclor 1248		0.0000173	0.0000163
Aroclor 1242		0.0000137	0.0000185
Aroclor 1254		0.0000099	0.0000131
Aroclor 1268		0.0000057	0.0000051
Aroclors 1260 and 1262	Active inducers, not quantified.		
Aroclor 1016		No induction.	
Aroclor 1221		No induction.	

Source: Kubiak (1988)

Based upon the information provided by extensive testing in wildlife populations and limited application to human health considerations, it would appear that the use of congener–specific analysis would offer far more specificity and enhanced resolution in research related to the effects of toxic substances. The idea of equating of the degree of toxicity with the quantity of total PCBs, PCDDs, or PCDFs observed is obviously in error. The availability of new analytic techniques capable of measuring low levels of these compounds by congener, coupled with AHH and EROD enzyme induction assays, offer the potential to consider observed investigative outcomes in the light of more reliable toxicity data using dioxin equivalents.

Ultimately for wide application of these techniques, it will be necessary to alter the regulatory requirements for analytical testing to include congener–specific methodologies, rather than the existing comparisons with Aroclor standards.

2.2.9 Future Research Needs

2.2.9.1 Introduction

It is clear that although progress is being made towards the identification of airborne water pollutants and understanding their biological effects in wildlife and humans, there remains much that needs to be done. The mechanisms of action and diversity of effects of most xenobiotics are still not completely understood. However, the power of basic scientific research has been demonstrated with the identification of carcinogens and their modes of action.

The dominance of cancer as the effect of primary concern in assessing the risk of pesticides is being challenged by new evidence of effects of chemicals on the nervous, immune, endocrine, and reproductive systems of laboratory animals, wildlife, and humans. The disease state, or effect, in this case is measured by loss of function rather than gross clinical endpoints. Furthermore, it is now perceived that functional deficits in humans as a result of exposure to the chlorinated compounds, PCBs and dioxins, occur at lower concentrations than those extrapolated in rodent models to cause cancer. Most of the research on developmental toxicity has been done on PCBs and dioxins and on only a few chlorinated insecticides. As a result, little is known about the non–cancer health effects of pesticides and especially herbicides, the largest portion on a weight basis of pesticides currently in use. Of concern, are the infrequent and occasional studies that have shown without a doubt that many of the widely used pesticides are capable of interfering with the development and function of one or more of the critical life systems. Because of the potential threat to wildlife and human populations of these findings it is imperative to establish the means to better understand the non–cancer health effects of (1) all pesticides in use, (2) those that have been banned or restricted, and (3) any new pesticides being registered. To delay could seriously affect the survival and well–being of future generations. As a result of the great diversity of effects, the complicated mechanisms of action, and the insidious nature of low–level exposures, increased and broad–based funding for innovative research on non–carcinogenic end–points and mechanisms in wildlife and humans is clearly warranted.

The following identified research needs are prioritized within general fields of research. However, the fields themselves are not prioritized, since all fields of research must progress together to achieve a proper understanding of the problem. These prioritized needs are intended to identify some of the more apparent gaps in our knowledge in each general field of research. Obviously, these lists can not be comprehensive, but they will serve as a guide for researchers and funding agencies alike.

2.2.9.2 Research Needs Related to Eutrophication

1. Atmospheric nitrogen is delivered to coastal waters both through direct deposition to the waters and through deposition on upstream watersheds followed by gradual downstream washout. The extent to which nitrogen deposited on watersheds is retained in the watershed rather than being exported downstream is very poorly known and probably varies greatly depending upon a variety of factors, including land use in the watershed and age of forest stands. Research on these factors is required if we are to better understand the importance of atmospheric nitrogen on coastal eutrophication. Such research may lead to control strategies beyond simply controlling atmospheric nitrogen emissions, such as managing forest growth or wetlands which fringe streams.

2. Increased nitrogen inputs are well known to be the dominant cause of eutrophication (overall increased algal growth, causing anoxia, hypoxia, and dieback of macrophyte beds) in many, perhaps most, of the estuaries and coastal waters of the United States. However, it is much less clear that nitrogen is the cause of the increased incidence of nuisance algal blooms by single species of algae (red tides and brown tides). Research is needed to determine: 1) if nitrogen alone is a proximate cause of blooms; 2) if eutrophication from increased nitrogen loading might result in the formation of nuisance algal blooms indirectly (for example by lowering the availability of silica or by increasing the extent of anoxic sediments); 3) if some other element such as iron or molybdenum must interact with nitrogen to trigger a bloom; or 4) if nitrogen has no relationship to bloom formation in the coastal Great Waters.

3. Most dose–response relationships for nitrogen and coastal eutrophication have dealt with annual time steps. However, it may be only necessary to control nitrogen deposition during some critical period of the growing season in some coastal Great Waters. The seasonal variation in the response of estuarine eutrophication to nitrogen inputs from atmospheric deposition requires further research. Factors to consider include the spatial and temporal patterns of nitrogen transport in the atmosphere, the residence time of nitrogen in watersheds, and the seasonality of phytoplankton production in estuaries.

4. Increased nitrogen inputs to many coastal waters and estuaries leads to increasing eutrophication and anoxia and hypoxia (low oxygen in the water column). Research is needed to determine if this increases the sensitivity of the biota to other stresses, such as those from toxic substances.

2.2.9.3 Research Needs for Ecosystem Level Effects of Xenobiotic Substances

Even though studies of the long-range atmospheric transport of toxic xenobiotic chemicals began as early as the mid-1970s, the scientific community only has a limited understanding of a variety of issues surrounding the central question. Upon reaching the aquatic or marine ecosystem, a further array of questions remain unanswered. Research on the spectrum of these issues is required if understanding of fate and transport of toxic chemicals is to be achieved.

1. Our present knowledge of the rate and magnitude of inputs of toxic substances to the world's Great Waters is extremely limited.

2. Additional research on sources of these contaminants is required, with special emphasis on differentiation between such issues as revolatilization, existing domestic sources, and transboundary pollution from foreign sources.

3. The contemporary understanding of deposition processes is limited. Additional research on the mechanisms involved in the entry of these compounds into waterbodies is required, as is study of the form of the materials entering the ecosystem. Recent studies suggest that some of the assumptions made about deposition processes have been incorrect. Additional studies are required for verification.

4. The understanding of the scientific community of the bioavailability of these chemicals is limited. Additional research is required to understand the fate of these compounds and the ultimate exposure of biota in the Great Waters. This knowledge would resolve the question of concentrations of chemicals versus the estimates of biota exposure.

5. Research addressing "new, relatively unstudied" contaminants, e.g., atrazine, entering the ecosystem, is required.

6. Research is needed on the effects of pH, temperature, salinity, and dissolved oxygen on: (1) the internal response of the organism; and (2) the effective dose to the organism.

7. Research is also needed on determining the assimilation efficiencies for a variety of chemicals in various organisms.

8. Additional field studies on the effects of these materials, particularly subtle effects, are required.

9. One of the most promising areas of research includes the integrated study approach incorporating fate assessment chemists, biologists, and toxicologists. These studies will assist in establishing and defining cause-effect linkages between airborne toxic compounds and receptor organism effects.

2.2.9.4 Research Needs for Wildlife and Human Health Effects from Xenobiotic Substances

1. Current research on most of the wildlife health problems and some of the human health problems induced by xenobiotic contaminants often results from serendipitous observations by scientists engaged in other field or laboratory studies. In the light of the present evidence, a new vehicle is needed to enable and encourage forensic research demonstrating the effects of chemicals in living organisms. The organization of this vehicle must encourage both field and laboratory studies in wildlife and human populations to satisfy the need for causal linkages.

2. This vehicle must promote innovative, multi-disciplinary research on transgenerationally-transmitted early markers of exposure that predict long-term, delayed, loss of function. These research efforts should be designed to determine the most sensitive endpoint(s) (the lower-limits of effect) using a multigenerational model.

3. The proposed vehicle must promote innovative, cross-discipline, multi-level (gene to ecosystem) research, that addresses pollution problems recognized as a result of damage in the field from ambient levels of xenobiotic compounds.

4. This vehicle should also establish a review process for research proposals that is geared to support the cutting edge research necessary to keep ahead of the technologies producing new and more powerful pesticides. This must be a new review process separate from the current practice in use today.

5. The vehicle should also fund the development of inexpensive, short-term screening techniques to test new and old products for endocrine, nervous, and immune system disruptive capacity.

6. This vehicle would serve to accelerate testing of banned and restricted products that still pose a threat to humans and wildlife because of their persistence and presence in human tissue.

7. In addition to considering human impacts directly, this vehicle should also support exposure and effect studies using free-ranging wildlife as models for human exposure and effects resulting from ambient levels of xenobiotic compounds.

8. Although we increasingly are beginning to understand the mechanism of action of toxic substances on the biology of individual organisms and on sub-organismal levels of biotic organization, the relationship of effect at these levels to effects at higher levels of biotic organization remain obscure. The proposed research vehicle should stimulate multi-disciplined research relating the effects of toxic substances on individual organisms to effects on populations, communities, and ecosystems.

Research Needs for the Mechanisms of Action of Xenobiotic Substances

1. There are a multiple of possible deleterious endpoints from xenobiotic exposure other than cancer. Research on diverse mechanisms of effect and the multiplicity of biological endpoints must be increased.

2. Some effects of xenobiotics are insidious, long-term, and multigenerational. An increase in long-term studies of single exposure, low-dose, or embryonic and developmental exposure is warranted.

3. The lower-limits of effects are unknown for virtually all chemicals, especially considering long-term and multigenerational studies. The establishment of lower-thresholds for all known effects must be undertaken.

4. Central to our establishment of guidelines for chemical usage and risk assessment is the understanding of the range of thresholds and effects within genetically diverse populations, and not merely the mean threshold levels for effects. The identification of thresholds for "sensitive" members of populations is warranted for future risk assessment decisions.

5. There are large gaps in our knowledge concerning the effects of xenobiotics in diverse groups of organisms, such as reptiles, amphibians, chondrichthian fishes (sharks, skates and rays), invertebrates and vascular plants. These groups form important parts of the food web and habitats they live in and, and many are showing world-wide declines, amphibians and sharks. An increased research emphasis is needed in these groups.

6. Wildlife and humans are exposed to a large diversity of chemicals. The interactions of multiple xenobiotic chemicals must be investigated in order to elucidate possible synergisms or antagonisms.

7. The influence of environmental factors, such as temperature, pH, salinity, and dissolved oxygen content are poorly understood with regards to how they modify xenobiotic toxicities. The study of environmental factors for diverse habits, such as warm-water lakes, estuaries, and tropical marches are clearly warranted.

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2.2.11 Animal Species

Beluga	*Delphinapterus leucas*
English sole	*Parophrys vetulus*
Rock sole	*Lepidopsetta bilineata*
Starry flounder	*Platichthys stellatus*
Flathead sole	*Hippoglossoides elassodon*
White croaker	*Genyonemus lineatus*
White perch	*Morone americana*
Windowpane flounder	*Scopthalmus aquosus*
Winter flounder	*Pseudopleuronectes americanus*
Bullhead trout	*Salvelinus confluentus*
Atlantic croaker	*Micropogonias undulatus*
California halibut	*Paralichthys californicus*
Dolly Varden	*Salvelinus malma*
Hornyhead turbot	*Scophthalmus maximus*
Pacific halibut	*Hippoglossus sp.*
Herring gull	*Larus argentatus*
Forster's tern	*Sterna forsteri*
Ring-billed gull	*Larus delawarensus*
Western gull	*Larus occidentalis*
California gull	*Larus californicus*
Pink salmon	*Onchorhynchus gorbuscha*
Coho salmon	*Onchorhynchus kisutch*
Chinook salmon	*Oncorhynchus tshawytscha*
Striped bass	*Morone saxatilus*
Sea star	*Asterias rubens*
Atlantic cod	*Gadus morhua*
Rainbow trout	*Salmo gairdneri*
Polychaete	*Nereis virens*
Mussel	*Mytilus edulis L.*
Caspian tern	*Hydroprogne caspia*
Bald eagle	*Haliaetus leucocephalus*
Black-crowned night-heron	*Nycticorax*
Common tern	*Sterna hirundo*
Double-crested cormorant	*Phalactrocorax auritus*
Osprey	*Pandion haliaetus*
Mink	*Mustela vison*
Otter	*Lutra canadensis*
Lake trout	*Sylvelinus namaycush*
Common snapping turtle	*Chelydra serpentina*
Great blue heron	*Ardea herodias*
Virginia rail	*Ralus virginianus*

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