The Wildlife/Human Connection: Modernizing Risk Decisions

Theo Colborn
World Wildlife Fund, Washington, DC

This article proposes that genetic and molecular ecotoxicology can play an important role in making policy and risk assessment decisions concerning xenobiotics. It calls for a greater awareness by ecotoxicologists to the effects in wildlife and humans resulting from transgenerational exposure to synthetic chemicals that interfere with gene expression and differentiation. The difficulty of recognizing these effects on the endocrine, immune, and nervous systems in developing embryos is described and suggests why effects of this nature have traditionally not been addressed when determining risk to synthetic chemicals. Specific examples are cited of environmental effects on hormonally responsive tissue in wildlife populations which could be used as models for assessing human exposure to synthetic chemicals. Evidence is presented that the environmental load of synthetic chemicals has reached critical levels at which wildlife and human health are at risk. — Environ Health Perspect 102(Suppl 12):55–59 (1994)

Key words: biodiversity, endocrine disruptors, dioxin, exposure, functionality, hormones, PCBs, policy, risk, wildlife, xenobiotics

Introduction

This article presents examples of environmental effects on hormonally responsive tissue in troubled wildlife populations that provide a model for assessing previously overlooked human health hazards associated with exposure to synthetic chemicals. The difficulty of recognizing these effects on the endocrine, immune, and nervous systems in wildlife and humans explains why the problems are usually not discovered until they become quantifiable at the population level. In the past, health effects of this nature were not addressed when determining the safety of synthetic chemicals. Consequently, endocrine-disrupting, synthetic chemicals once considered benign are now an integral part of the global ecosystem posing an emerging threat to biodiversity.

The number of synthetic chemicals that are capable of disrupting the endocrine system continues to grow as they are serendipitously (1,2) or deliberately (3) discovered. Among the chemicals are fungicides, insecticides, herbicides, components in plastics and detergents, and other industrial products and by-products (4). These manmade chemicals look like, or interfere with, endogenously produced hormones, neurotransmitters, growth factors, and inhibiting substances. They invade the environment of the embryo and change its course of development (5). Effects not often expressed overtly in the parent are manifested as second generation sequelae of changes in the architecture and function of the endocrine, immune, and nervous systems of offspring exposed during critical periods of organ development (5).

A number of the endocrine disruptive effects reported in wildlife populations have been replicated in confined wild animals (6,7) and laboratory animals using single xenobiotics (3,8). However, in the real world, exposure involves multiple xenobiotics making causal links difficult. The effects are not necessarily expressed as gross physical defects that are visibly recognizable, but instead are expressed as losses of function which until recently have not been described. Consequently, with wildlife and humans alike, a generation may pass before the effects become apparent, and only after the problem is widespread and has reached population proportion (9,10).

Many of the persistent endocrine-disrupting xenobiotics are found in the reproductive tissues of animals, including humans (11). However, recent findings that only one, very low, dose of dioxin administered during gestation can change the sexual development of rat offspring demonstrate that a xenobiotic need not be persistent nor bioaccumulative to interfere with the development of vital systems. Timing of exposure during gestation is critical (8). These recent dioxin studies also emphasize the importance of broadening testing protocols for all chemicals destined to become a part of commerce that will come in contact with large numbers of wildlife and humans. Short-lived chemicals that "hit and run" might never be linked with in utero damage unless they are carefully screened via multigenerational studies designed to detect functional changes. Unfortunately, the current substitutes for the older, more persistent bioaccumulative chemicals, such as the DDT and PCB analogs, have not been screened for their disruptive effects on the differentiation of organ systems.

Wildlife

A comprehensive review of the literature on the health status of birds, fishes, mammals, and reptiles in the northern hemisphere reveals widespread instability, decline, and extinction among populations (12,13). Among those animals that can reproduce, however, aberrant development expressed in their offspring often goes unseen because the young are kept in seclusion, making it difficult to build a case for research in functional teratology. To date, some of the most convincing wildlife research on transgenerational loss of function has been accomplished during the breeding season among nesting colonies of egg-laying species [(14); T Gross, L Guillette, personal communication, re: turtles and alligators]. Compared with the geographic scope and seriousness of the problem, however, there has been little support for research to determine the cause of the problems. Perhaps this is because infertility among adult animals that leads to population attrition is difficult to detect and does not catch the interest of public health authorities and funding sources compared with more obvious diseases such as cancer.
Follow-up studies on troubled wildlife populations have revealed a number of conditions associated with reproductive success. Depending upon the species and study designs, these have been measured as reductions in embryo hatchability (15) and viability (16); chick (17) and fry survivorship (18); egg size and numbers (19); numbers of animals reaching sexual maturity (20); production of endogenous hormones, such as thyroid hormones (7,21), estrogen (22), testosterone (23,24), and retinoids (7), as well as immune-competency. Increases in thyroid (25) and liver size (17); liver enzyme induction (17); highly carboxylated porphyrins (26); numbers of animals exhibiting sex reversal (6,27,28); spontaneous abortions (29); hermaphroditism (30); sex-linked birth defects; asymmetrical brains (31) and skulls (32); and unusual behavior (17,33) have been reported as well. Regarding sex-linked birth defects, M Fry (personal communication) has reported that in a study of crossed-billed double-crested cormorants, the birth defects all were in phenotypic females (n = 100). In another study, of crossed-billed bald eagles discovered in 1993, all birth defects were in females (T Kubiak, personal communication; n = 3).

The above effects are not the result of mutations, but are epigenetic in nature. They are the result of changes in gene expression through many mechanisms, such as blockage, modulation, or improper timing, the results of which are unpredictable in most cases (34). Scientists and regulators have sought mutational answers to the problem because of the need for quantifiable standards for regulatory purposes and to respond to society’s fixation on cancer. However, current standards and testing protocols for synthetic chemicals need to be reevaluated, opening new research opportunities for molecular and genetic ecotoxicologists. Obviously more needs to be learned about the mechanism of action of endocrine disruption.

The large-scale mortality among dolphin, porpoise, seal, and whale populations commencing in 1987 (35–38) has generated a number of questions. Why, suddenly in one year in widely disconnected geographic regions in the northern hemisphere should this occur? In this case, long-lived, toothed mammals that are obligate fish-eaters exhibited symptoms of immune incompetency and were affected by new strains of viruses (one specific to dolphins, another to seals, and another to porpoises) or by naturally produced marine toxins (39).

In an effort to explain the sudden onset of marine mammal die-offs, it is important to keep in mind that mature animals in the first generation exposed to xenobiotics generally do not display obvious effects as a result of their exposure (40). If the trans-generational hypothesis holds, wide-scale immune incompetency would not appear until the second generation (41,42). Were those mammals that succumbed in the recent die-offs second generation individuals whose endocrine and immune systems were constructed differently because of in utero exposure to xenobiotics? And were some of the older animals that died individuals whose immune systems had reached threshold levels of effect as the result of years of high-dose exposure? These animals held some of the highest concentrations of organochlorine chemicals ever reported (43).

The Human Connection

Table 1 provides an historical perspective on widespread exposure to xenobiotics for humans, a long-lived species, and may provide a clue to the marine mammal problem. PCBs were first manufactured and used in 1929, DDT in 1938. The 1940s are often referred to as the birth of the chemical revolution, driven by new technology during and immediately following World War II (44). It was during this period that humans (with a generation time of approximately 20 years) were first exposed to a vast number of chemicals. By the mid-1960s these individuals began to bear children and produced the first generation of humans exposed to xenobiotics in utero—the first generation born with xenobiotics in their tissues. About 1980 this generation reached reproductive age.

In the case of long-lived marine mammals, the timing of the recent mass mortalities fits the above exposure model when factoring in the delay between initial production and use of xenobiotics on land and their reaching the oceans, plus the tremendous dilution factor of the marine systems. The marine mammals that suffered the die-offs have generation times of approximately 10 to 15 years and are indigenous to highly contaminated enclosed aquatic regions, such as coastal waters and the Baltic and Mediterranean seas.

In the past, human epidemiologic studies designed to determine the outcome of exposure to a xenobiotic(s) have questioned only the health of the exposed individuals. It is not surprising that many human studies have failed to link adverse health effects with exposure to xenobiotics (Type II errors). The lesson learned from wildlife reveals the importance of considering the health of the offspring of the exposed individuals. For example, when seeking causal links for loss of fertility or immune competency among cohorts, the subjects’ prenatal and early postnatal exposure must be considered (in other words, what was their parents’ exposure to xenobiotics?). Prenatal and perinatal exposure to xenobiotics probably have more influence on fertility than any other exposure throughout a lifetime. Functional deficits derived from in utero exposure in many cases may not correlate with only postnatal exposure. Most important, in light of the widespread distribution of these chemicals in the environment, it may be too late to find unexposed populations.

Evidence is building that xenobiotics are present in humans at concentrations that are toxicologically relevant. For instance, female seals exposed to 27 µg/kg/body weight (bw)/day PCB on a Wadden sea fish diet were less productive than seals exposed to 8 µg/kg (bw)/day on a North Atlantic fish diet (45). They experienced reduced plasma retinol and fewer implantations and were more prone to abort and develop uterine occlusions. The Wadden Sea population of seals collapsed from 3000 to 500 animals between 1950 and 1975. Female mink, animals who, like seals, also have delayed implantation, suffered similar and more severe effects when exposed to 25/µg/kg (bw)/day PCBs (46). Similarly, it was estimated that the mothers of children who experienced impaired visual recognition memory at 7 months and short-term memory problems at 4 years were delivering a dose of >27 µg/kg (bw)/day PCBs to their offspring (47).

| Time span | Exposure event |
|-----------|----------------|
| 1929      | PCBs introduced |
| 1938      | DDT first manufactured |
| 1940s-1950s | FIRST WIDE SCALE EXPOSURE TO MAN-MADE CHEMICALS |
| 1950s-1970s | First generation exposed postnataally |
| 1970s-1990s | First generation exposed in womb |
|  | |

56 Environmental Health Perspectives
the same study it was also estimated that 
the mothers (from Michigan) were exposed to 
0.093 µg/kg (bw)/day PCB throughout their 
life preceding pregnancy, which provides a model of the persistence of the 
PCBs. By comparison, 52.5% of Inuit 
women in eastern Arctic Canada participating 
in seven food consumption surveys are 
exposed to 0.25 to 3.25 µg/kg (bw)/day PCB (48). 
Suckling infants consuming 
breast milk at the U.S. average of 0.8 to 1 
ppm PCB in milk fat are exposed to 5 
µg/kg (bw)/day PCB, five times the 
Allowable Daily Intake (ADI) set by the 
Food and Agricultural Organization for a 
70 kg adult (49). The parents of the 
children in the Japanese rice oil incident 
(contaminated with PCBs and furans) were 
exposed to 63 µg/kg (bw)/day PCB for 
three months (50), about 100 times the 
lifetime dose of the Michigan mothers.

The average U.S. adult's body burden 
of dioxin (2,3,7,8-TCDD), is approximately 
7 to 10 ppt. Dioxin’s ability to 
induce cytochrome P450 enzymes in rat 
 liver hepatoma cells (H4IIIE) has been used 
as a surrogate to describe its toxicity. Using 
dioxin as the standard for CP450 activity 
on a weight-to-weight basis one can either 
measure directly or calculate (using equival- 
cency factors times concentration) the 
toxicity of other dioxinlike compounds in 
tissue. The combined 2,3,7,8-TCDD, 
dioxin and furan isomers, and coplanar 
PCBs in the average adult's body are 
equivalent to 50 dioxin enzyme toxicity 
equivalents (TEQs). This is very close to the 64 
ppb of pure 2,3,7,8-TCDD fed to pregnant 
rats whose male pups experienced abnor-
mal sexual development, sperm count 
reduction, and behavioral changes (8). A 
recent French report found five coplanar 
PCB congeners (total 170 ppb) in human 
 breast-milk fat that on an H4IIIE basis are 
equivalent to 6397 2,3,7,8-TCDD TEQs 
(51). The breast-milk fat held 1.01 ppm 
total PCBs which is similar to the US aver-
age of 1 ppm. In addition, the milk held 
307 ppbs of five PCB congeners [numbers 
28 (52), 52 (53), 138 (54), 153 (52.54), 
169 (55)] that also disrupt the endocrine 
system and reproductivity. Double-crested 
cormorants exhibit significant increases in 
embryonic mortality when their eggs hold 
approximately 100 dioxin TEQs using the 
H4IIIE assay, with measurable losses com-
mencing at about 40 or 50 TEQs (16).

A number of laboratory studies suggest 
that fertility among human populations, 
like wildlife populations, when exposed to 
ubiquitous xenobiotics may be at risk. 
For example, in repeated trials it was demon-
strated that the sperm of mature male rats 
exposed to PCBs postnatally through breast 
milk have difficulty penetrating ova or 
maintaining a viable zygote (56). In 
another study, pregnant rats fed one meal 
of dioxin [0.064, 0.16, 0.4, and 1.0 µg/kg 
(bw)] on day 15 of gestation gave birth to 
 male offspring who were demasculinized 
and feminized, as determined bymorpho-
logical, biochemical, physiological, and 
behavioral parameters; their sperm count 
was also reduced 75% (8). Many of the 
effects were not measurable until the pups 
matured. In a follow-up study (1.0 µg/kg 
bw) female pups exhibited morphological 
changes in external genitalia at birth and a 
sequelae of changes in the reproductive 
tract that were similar to effects reported in 
mice and humans exposed in utero to 
diethylstilbestrol (DES) (L Birnbaum, LE 
Gray, personal communication, 1993).

The motility of sperm from men expe-
rriencing fertility problems (<20 million 
sperm/ml) was inversely proportional to 
the concentration of three PCB congeners 
in their semen; 2,4,5,2',4',5'-hexa- 
(no.153), 2,4,5,2',3',4'-hexa-(no. 138), 
and 2,4,5,3',4'-pentachlorobiphenyl (no. 
114) (53). All three congeners are com-
monly found in human breast milk (57). 
Congener 153 comprises approximately 
20% of the PCB body burden of living 
people living in industrialized temperate areas and 
40 to 50% of the body burden of native 
Americans living in eastern Arctic Canada 
(58,59). A meta-analysis that reexamined 
61 sperm-count studies revealed that 
worldwide sperm count has decreased by 
approximately 50% since 1938 (9). A dou-
bling of cryptorchidism occurred in the 
United Kingdom between 1970 and 1987 
(60,61). Realizing that these effects could 
be the result of exposure to elevated 
endocrine-disrupters during prenatal de-
velopment, it has been suggested that the 
cause may be from environmental contami-
nants (62,63). A significant reduction in 
penis size at puberty, among other prob-
lems, has been associated with prenatal 
exposure to PCBs and furans among the 
offspring of women who consumed PCB 
contaminated rice oil in Taiwan (64).

**Recommendations**

Wildlife and humans are signaling prob-
lems at the population level that biodiver-
sity is at risk. Addressing the problem with 
laboratory animal studies on a chemical-by-
chemical basis will not work. The additive 
(A Soto, personal communication), syner-
gistic, and other interactive (65) effects of 
chemicals already in the environment can- 
not be predicted. For ecotoxicology to 
meet these challenges it must:

- be more aware of and develop protocols 
  to assess functional damage in the field;
- test in the laboratory the hypotheses gen-
  erated in the field concerning causal 
  links between wildlife damage and 
  chemicals;
- find early markers in developing tissue 
  that predict long-term delayed effects on 
  functionality for both wildlife and 
  humans;
- test the hypothesis that there are links 
  between cell differentiation during de-
  velopment and cancer;
- break disciplinary boundaries, reach out, 
  and collaborate with those responsible 
  for public health; and
- convince the policy/risk community that 
  field data have a role in its deliberations.

With this agenda in place ecotoxicology 
could bring a "real-world approach" to 
decision tables.

**REFERENCES**

1. Soto AM, Lin TM, Justica H, Silvia, RM, Sonnenschein C. An “in culture" bio-assay to assess the estrogenicity of xenobiotics (E-SCREEN). In: Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection (Colborn T, Clement C, eds). Princeton, NJ:Princeton Scientific Publishing, 1992:295–310.
2. Krishnan AV, Stathis P, Permutt SF, Toles L, Feldman D. Bisphenol-A: an estrogenic substance is released from polycarbonates flasks during autoclaving. Endocrinology 132(6):2279–2286 (1993).
3. Gray LE. Chemical-induced alterations of sexual differentiation: a review of effects in humans and rodents. In: Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection (Colborn T, Clement C, eds). Princeton, NJ:Princeton Scientific Publishing, 1992:203–230.
4. Colborn T, vom Saal F, Soto A. Developmental effects of endocrine-disrupting chemicals in wildlife and humans.
Environ Health Perspect 101(5):378-384 (1993).
5. Colborn T, Clement C, eds. Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection. Princeton, NJ:Princeton Scientific Publishing, 1992:195-202.
6. Fry DM, Toone CK. DDT-induced feminization of gull embryos. Science 231:919-924 (1981).
7. Brouwer A, Reijnders PJH, Koeman JH. Polychlorinated biphenyl (PCB)-contaminated fish induces vitamin A and thyroid hormone deficiency in the common seal, Phoca vitulina. Aquat Toxicol 15:99-106 (1989).
8. Mably TA, Dallaire RW, Bjørke DL, Peterson RE. The male reproductive system is highly sensitive to in utero and lactational TCDD exposure. In: Biological Basis for Risk Assessment of Dioxins and Related Compounds (Gallo MA, Scheuplein RJ, van der Heijden CA, eds). Cold Spring Harbor, NY:Cold Spring Harbor Laboratory Press, 1991:69-78.
9. Carlsen E, Giwercman A, Kreiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. Br Med J 304:609-613 (1992).
10. Risebrough RW, Peakall DB, Herman SG, Kirven MN. Polychlorinated biphenyls in the global ecosystem. Nature 220:1098-1102 (1968).
11. Thomas KF, Colborn T. Organochlorine endocrine disruptors in human tissue. In: Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection (Colborn T, Clement C, eds). Princeton, NJ:Princeton Scientific Publishing, 1992:365-394.
12. Colborn T. Epidemiology of Great Lakes bald eagles. J Toxicol Environ Health 33:395-453 (1991).
13. Colborn T. Great Lakes Toxics Working Paper. Contract no KE144-7-6336. Hull, Quebec: Environment Canada. April 1988.
14. Kubiak TJ, Harris HJ, Smith LM, Schwartz TR, Stalling DL, Trick JA, Sileo L, Doucherty DE, Erdman TC. Microcontaminants and reproductive impairment of the Forster's tern on Great Bay, Lake Michigan—1983. Arch Environ Contam Toxicol 18:706-727 (1989).
15. Mac M, Schwartz T, Edsall C. Correlating PCB effects on fish reproduction using dioxin equivalents. Paper presented at Ninth Annual SETAC Meeting, Arlington, VA (1988).
16. Tillit DE, Ankley GT, Giessy JP, Ludwig JP, Kurita-Matsuba H, Weseloh DV, Ross PS, Bishop CA, Sileo L, Stromberg KL, Larson J, Kubiak TJ. Polychlorinated biphenyl residues and egg asymmetry in double-crested cormorants from the Great Lakes. Environ Toxicol Chem 11:1281-1288 (1992).
17. Kubiak T, Harris H, Smith L, Schwartz T, Stalling D, Trick J, Sileo L, Doucherty D, Erdman T. Microcontaminants and reproductive impairment of the Forster's tern on Green Bay, Lake Michigan—1983. Arch Environ Contam Toxicol 18:706-727 (1989).
18. Walker MK, Peterson RE. Toxicity of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls during early development in fish. In: Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection (Colborn T, Clement C, eds). Princeton, NJ:Princeton Scientific Publishing, 1992:195-202.
19. McMaster ME, Portt CB, Munckitrick KR, Dixon DG. Milt characteristics, reproductive performance, and larval survival and development of white sucker exposed to bleached kraft mill effluent. Ecotoxicol Environ Saf 23:103-117 (1992).
20. Leatherland, JF. Endocrine and reproductive function in Great Lakes salmon: In: Chemically Induced Alteration in Sexual and Functional Development: The Wildlife/Human Connection (Colborn T, Clement C, eds). Princeton, NJ:Princeton Scientific Publishing, 1992:129-146.
21. Leatherland JF, Lin L, Down NE, Donaldson EM. Thyroid hormone content of eggs and early developmental stages of three stocks of coho salmon (Oncorhynchus kisutch) from the Great Lakes of North America, and a comparison with a stock from British Columbia. Can J Fish Aquat Sci 46:2146-2152 (1989).
22. Munckitrick KR, Portt CB, Van Der Kraak GJ, Smith IR, Rokosh D. Impact of bleached kraft mill effluent on population characteristics, liver MFO activity, and serum steroid levels of a Lake Superior white sucker (Catosomus commersonii) population. Can J Fish Aquat Sci 48:1371-1380 (1991).
23. Munckitrick KR, Van Der Kraak GJ, McMaster ME, Portt CB. Response of hepatic MFO activity and plasma sex steroids to secondary treatment of bleached kraft pulp mill effluent and mill shutdown. Environ Toxicol Chem 11:1427-1439 (1992).
24. Subramanian A, Tanabe S, Tatsukawa R, Saito S, Mirzazaki N. Reductions in the testosterone levels by PCBs and DDDE in Dall's porpoises of northwestern North Pacific. Marine Pollut Bull 18(12):643-646 (1987).
25. Mocca RD, Leatherland JF, Sonstegard RA. Quantitative interlake comparison of thyroid pathology in Great Lakes coho (Oncorhynchus kisutch) and chinook (Oncorhynchus tschawytscha) salmon. Cancer Res 41:2200-2210 (1981).
26. Fox G, Kennedy S, Norstrom R, Wigfield D. Porphyria in her-ring gulls: a biochemical response to chemical contamination of Great Lakes fish food chains. Environ Toxicol Chem 7:831-839 (1988).
27. Gibbs PE, Pascoe PL, Burt GR. Sex change in the female dog-winkle, Nucella lapillus, induced by tributyrin from antifouling paints. J Mar Biol Assoc UK 68:715-731 (1988).
28. Davis WP, Bortone SA. Effects of kraft mill effluent on the sex of fishes: an environmental early warning? In: Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection (Colborn T, Clement C, eds). Princeton, NJ:Princeton Scientific Publishing, 1992:113-148.
29. Reijnders PJH. Reproductive failure in common seals feeding on fish from polluted coastal waters. Nature 324:456-457 (1986).
30. DeGuise S, Lagace A, Beland P. Hermaphroditism in a beluga whale. J Wildlife Dis 30(2):287-290 (1994).
31. Henshel DS, Cheng KM, Norstrom R, Whitehead P, Steeves JD. Morphometric and histologic changes in brains of great blue heron hatchlings exposed to PCDDs: preliminary analysis. In: Environmental Toxicology and Risk Assessment: Aquatic, Plant, Terrestrial Symposium. ASTM STP 1179 (Landis WG, Hughes JS, Lewis MA, eds). Philadelphia:American Society for Testing and Materials, 1993:262-277.
32. Zakharov VM, Yablokov AV. Skull asymmetry in the Baltic grey seal: effects of environmental pollution. Ambio 19(5):266-269 (1990).
33. Shugart G. Frequency and distribution of polygyny in Great Lakes herring gulls in 1978. Condor 82:426-429 (1980).
34. Gray LE, Ostby J, Ferrell J, Signon R, Cooper R, Linder R, Rehnberg G, Goldman J, Laskey J. Correlation of sperm and endocrine measures with reproductive success in rodents. In: Sperm Measures and Reproductive Success. Institute for Health Policy Analysis. Forum on Science, Health and Environmental Risk Assessment. New York:Alan R Liss, Inc., 1989:193-209.
35. Simmonds M. What future for European seals now the epidemic is over? ORXY 25(1):27-32 (1991).
36. Dietz R, Heid-Jorgensen MP, Harkonnen T. Deaths of harbor seals in Europe. Ambio 18(5):258-264 (1989).
37. Oehme O, Ryg M, Furst P, Furst C, Meemken HA, Groebel W. Reevaluation of concentration levels of dioxin and furan in Arctic seal from Spitzbergen. Chemosphere 21(4-5):519-523 (1990).
38. Kuehl DW, Haebeler R, Patter C. Chemical residues in dolphins from the U.S. Atlantic coast including Atlantic bottlenose obtained during the 1987/88 mass mortality. Chemosphere 22(11):1071-1084 (1991).
39. Geraci JR. Investigation of the 1987-1988 Mass Mortality of Bottlenose Dolphins Along the U.S. Central and South Atlantic Coast. Final Report to National Marine Fisheries Service and U.S. Navy, Office of Naval Research and Marine Mammal Commission (1989).
40. McLachlan JA, Newbould RR, Teng CT, Korach KS. Environmental estrogens: orphan receptors and genetic
imprinting. In: Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection (Colborn T, Clement C, eds). Princeton, NJ:Princeton Scientific Publishing, 1992;107–112.

41. Blair PB, Noller KL, Turul J, Forghani B, Hagens S. Disease patterns and antibody responses to viral antigens in women exposed in utero to diethylstilbestrol. In: Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection (Colborn T, Clement C, eds). New Jersey:Princeton Scientific Publishing, 1992;283–288.

42. Blair, PB. Immunologic studies of women exposed in utero to diethylstilbestrol. In: Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection (Colborn T, Clement C, eds). Princeton, NJ: Princeton Scientific Publishing, 1992;289–293.

43. Tanabe S, Tatsukawa R. Persistent organochlorines in marine mammals. In: Organic Contaminants in the Environment: Environmental Pathways and Effects (Jones KC, ed). New York: Elsevier Applied Sciences, 1991;275–289.

44. Ihde A. The Development of Modern Chemistry. New York: Harper and Row, 1970.

45. Reijnders P. Reproductive failure in common seals feeding on fish from polluted coastal waters. Nature 324:456–457 (1986).

46. den Boer MH. Reproduction decline of harbor seals: PCBs in the food and their effect on mink. Annual Report. Leersum, Netherlands: Research Institute for Nature Management, 1983;77–86.

47. Tilson HA, Jacobson JL, Rogen WJ. Polychlorinated biphenyls and the developing nervous system: cross-species comparisons. Neurotoxicol Teratol 12:239–248 (1990).

48. Kinlock D, Kuhnlein H, Muir DC. Inuit foods and diet: a preliminary assessment of benefits and risks. Sci Total Environ 122:247–278 (1992).

49. ATSDR. Toxicological Profile for Selected PCBs (Aroclor-1260, -1254, -1248, -1242, -1232, -1221, and -1016). Washington: U.S. Department of Health and Human Services, 1987.

50. Isono N, Fujiwara K. Environmental pollution by PCB. Toxicity in the living body. Kagaku (Tokyo) 42:396–346 (1992).

51. Bordet F, Mallet J, Maurice L, Borrel S, Venant A. Organochlorine pesticide and PCB congener content of French human milk. Bull Environ Contam Toxicol 50:425–432 (1993).

52. Ness DK, Schantz SL, Mostaghian J, Hansen LG. Effects of perinatal exposure to specific PCB congeners on thyroid hormone concentrations and thyroid histology in the rat. Toxicol Lett 68:311–323 (1993).

53. Jansen HT, Cooke PS, Porcelli J, Liu T-C, Hansen LG. Estrogenic and antiestrogenic actions of PCBs in the female rat: in vitro and in vivo studies. Reprod Toxicol 7:237–248 (1993).

54. Bush B, Snow J, Koblitz R. Polychlorinated (PCB) congeners, p,p'-DDE, and sperm function in humans. Arch Environ Contam Toxicol 15:333–341 (1986).

55. Morse DC, Koeter HBWM, Smits van Prooijen AE, Brouwer A. Interference of polychlorinated biphenyls in thyroid hormone metabolism: possible neurotoxic consequences in fetal and neonatal rats. Chemosphere 25(1–2):165–168 (1992).

56. Sager DB, Shih-Schroeder W, Girard D. Effect of early postnatal exposure to polychlorinated biphenyls (PCBs) on fertility in male rats. Bull Environ Contam Toxicol 38:946–953 (1987).

57. Safe S, Safe L, Mullin M. Polychlorinated biphenyls: congener-specific analysis of a commercial mixture in human milk extract. J Ag Food Chem 33(1):24–29 (1985).

58. Dewailly E. Premeeting Comments. Workshop on Developmental Neurotoxic Effects Associated with Exposure to PCBs. Research Triangle Park, NC, September 14–15, 1992.

59. Dewailly E, Ayotte P, Bruneau S, Laliberte C, Muiir DC, Norstrom RJ. Human exposure to polychlorinated biphenyls through the aquatic food chain in the Arctic. Dioxin 93—13th International Symposium on Chlorinated Dioxins and Related Compounds. Vienna, September 1993. In: Organohalogen Compounds. 14:173–175 (1994).

60. Chivers, C, Forman D, Pike MC, Fogelman K, Wadsworth M. Apparent doubling of frequency of undescended testis in England and Wales 1962–1981. Lancet i:330–332 (1984).

61. Jackson MB, Chivers C, Pike, MC, Ansell P, Bull D. Cryptorchidism: an apparent substantial increase since 1960. Br Med J 293:1401–1404 (1986).

62. Sharpe RM, Skakkebaek NE. Are estrogens involved in falling sperm count and disorders of the male reproductive tract? Lancet 341:1392–1395 (1993).

63. Sharpe RM. Declining sperm counts in men— is there an endocrine cause? J Endocrinol 136:357–360 (1993).

64. Guo YL, Lai TJ, Ju SH, Chen YC, Hsu CC. Sexual developments and biological findings in Yucheng children. Dioxin 93—13th International Symposium on Chlorinated Dioxins and Related Compounds. Vienna, September 1993. In: Organohalogen Compounds. 14:235–238 (1994).

65. Porter WP, Green SM, Debbink NL, Carlson I. Groundwater pesticides: interactive effects of low-level concentrations of carbamates, aldicarb, methomyl, and the triazines, metribuzin on thyroxine and somatotropin levels in white rats. J Toxicol Environ Health 40:15–34 (1993).