ENVIRONMENTAL HEALTH PERSPECTIVES JAN 1995



March 23, 1994
pestpap.213 DRAFT

# PESTICIDES - HOW RESEARCH HAS SUCCEEDED AND FAILED IN INFORMING POLICY: ENDOCRINOLOGICAL EFFECTS ON WILDLIFE

Theo Colborn

World Wildlife Fund

1250 24th Street NW

Washington, DC 20037

PH 202 778 9643 FAX 202 861 8377

## INTRODUCTION

Over the past 40 years the research community provided evidence that a number of pesticides and industrial chemicals have disruptive effects on the endocrine system, especially during embryonic development. If the latter is true, why then has research not been able to translate this message into policy to prevent chemicals of this nature from entering commerce? This paper will provide an argument that the blame cannot be placed solely on the research community, but, instead, on the current research agenda of the institutions dedicated to protect and restore human and wildlife health.

As toxicological research became institutionalized in response to society's concern about cancer and acute mortality following exposure to pesticides and industrial chemicals, it became driven by risk assessment. As a result, research focused on the need for testing (data development) and the standardization of testing(1). Protocols were established to determine the probability of a

chemical causing cancer, acute mortality, visible birth defects, skin and eye irritation, and obvious neurotoxicological effects. Even though wildlife populations were recognized as harbingers for pesticide damage in humans as early as the 1960s(2), the science was ignored by those charged with protecting human health. The devastating effects of cancer so overwhelmed society, that the insidious legacy of toxic chemicals being transferred to our children was overlooked at that time. Despite this, the fascination with cancer was successful in removing a number of most egregious pesticides and industrial chemicals from the market and preventing others from becoming introduced in commerce. And by restricting the production and use of these suspected carcinogens, seriously affected wildlife populations experienced some relief and rebounded(3).

It was not until the late 1980s following an intense review and synthesis of the wildlife literature that the importance of wildlife health endpoints as models for human health was again proposed(4). There was growing concern arising from the evidence that freshwater, marine, and terrestrial wildlife populations from widespread geographic regions were still experiencing reproductive problems. Outright mortality (acute toxicity) was not the case. Instead, adult animals appeared to be healthy, but their offspring were plagued with a suite of effects that suggested abnormal development of vital physiological systems. This led to early death among offspring or loss of fertility if they survived to adulthood. Such demographic shifts are the underlying reason for population instability.

Concern for what these findings might mean for humans prompted the gathering of 21 scientists from 17 disciplines at the Wingspread Conference Center, Racine, Wisconsin, US in July 1991. The participants shared their knowledge relevant to the topic of the work session, "Chemically Induced Alterations in Sexual Development: The Wildlife/Human Connection". After having heard from each other the group issued a Consensus Statement(5) in which they were

> "...certain that a large number of man-made chemicals had been released into the environment that were capable of disrupting the endocrine systems of wildlife and humans.", and that
>
> "...if the environmental load of man-made endocrine disuptors was not abated, widespread dysfunction at the population level would take place."

Among their conclusions they also stated that

> "It is urgent to move reproductive effects and functional teratogenicity to the forefront when evaluating health risks. The cancer paradigm is insuffient because chemicals can cause severe health effects other than cancer."

They called for changes in testing to include

> "...hormonal activity in vivo.", "Integrated cooperative research ... to develop both wildlife and laboratory models for extrapolating risks to humans."

In essence they were calling for the institutionalization of essential forensic research (environmental detective work) that integrates multidisciplinary research both in the field and the laboratory to meet the challenge of a global environment dusted with manmade chemicals.

Under our present, reactive, regulatory system, proof of causality is essential prior to action. Consequently, it is imperative to determine damage from pesticides in wildlife and/or humans in the environment, and to return to the laboratory and recreate this damage. Currently, no federal institution has the mandate to synthesize the literature available on the non-cancer health effects of pesticides to determine what the damage might be and then undertake the necessary environmental detective work to determine if damage is occurring to wildlife or humans. Instead, the system has been locked into the traditional risk assessment strategy of testing pesticides on a chemical-by-chemical basis to determine what are considered allowable levels in the environment.

After 50 years of repeated warnings by scientists, the dominance of cancer as the effect of primary concern in assessing the risk of pesticides and other synthetic chemicals is being challenged by evidence of effects of chemicals on the nervous,

immune, endocrine, and reproductive systems of laboratory animals, wildlife, and humans(6,7). The disease state, or effect, in this case is measured by loss of function of one or more of these systems rather than obvious, physical deformities, outright mortality, or cancer. The bulk of the literature from this new effects-research has focused primarily on the developmental toxicity of three industrial chemicals, PCBs, dioxins, and furans, and on only a few chlorinated pesticides such as DDT, its metabolites and analogs. As a result, little is known about the non-cancer health effects of most pesticides and especially herbicides, the largest portion on a weight basis of pesticides currently in use in the US(8).

**THE WILDLIFE MESSAGE**

The scientific community has documented the endocrine disruptive effects of pesticides for almost 50 years, though little attention was paid to the message. For example, in 1950, Burlington and Lindeman(9) first reported that DDT behaved like the female hormone, estrogen. DDT fed to newly hatched male chicks prevented them from growing combs and wattles and reaching sexual maturity. Shugart(10) and Fox(11) later reported the occurrence of female-female pairing in colonial nesting birds which had elevated levels of DDT and other organochlorine chemicals. Fry and coworkers(12,13) in the early 1980s reported that DDT, its metabolites and analogs, kelthane, dicofol, and methoxychlor, caused male birds to grow oviductal tissue and be deprived of their

dominant male behavioral characteristics. Guillette(14) reported in 1994 that Florida alligators and turtles were suffering from an estrogen-like effect, probably as a result of exposure to DDE, a metabolite of dicofol. The male alligators have shortened phalluses (penises) making them physically incapable of breeding successfully. Slider turtles sharing the same nesting mounds around Lake Apopka become either females or intersex, a blend of both sexes. Functionally normal males were absent. Except for DDT, the other pesticides, kelthane, dicofol, and methoxychlor are still in production and use in the US. Despite warnings from the research community, all of the above pesticides, including DDT, are used on a global scale today.

Over the years researchers have reported a number of other reproductive problems among wildlife populations in the Northern Hemisphere that reflect disruption of the endocrine system (See Table 1). Disruption was expressed as changes in functionality across species from terrestrial to marine animals. Oftentimes the effects were not recognized until they reached population proportion.

In most cases the responsibility for the above effects was not assigned to a single chemical for several reasons: (1) because so many chemicals are present simultaneously in the environment, (2) separating effects is impossible because many chemicals cause similar damage, and (3) complementary laboratory research was not possible because of the high cost of organic chemical analyses.

## MECHANISMS OF ACTION: COMPLICATING THE RISK PARADIGM

Taking advantage of high-technology (analytical chemistry, sophisticated microscopy, super computers, sensitive analytical assays) scientists are recording changes that take place at the molecular and cellular level under both normal conditions in the presence of internally produced chemicals (hormones, neurotransmitters, growth factors, and inhibiting substances) and under abnormal conditions, in the presence of toxic chemicals (pesticides and industrial chemicals) (8). Scientists have repeatedly documented the scrambling of normal hormonal signals by pesticides in vivo and in vitro(15). This "mechanism of action" approach has provided answers to how certain toxic chemicals affect various tissues, organs, and systems and how chemicals affect whole organisms. However, considering the number of chemicals widely released in the environment today, it will be improbable to determine the mechanisms of action of all the chemicals in use.

The results of extensive research on the effects of diethylstilbestrol (DES), a synthetic estrogenic pharmaceutical that was administered to several million women between 1948 and 1971, provides parallels with effects that have been reported in wildlife and humans as a result of exposure to PCBs, dioxin, and DDT(16). Many of the disruptive effects of DES have been documented in laboratory rat and mouse embryos and thus provide an excellent model for the effects of other estrogen-like compounds on humans and wildlife(17). The literature on DES, similar to that on PCBs, dioxins, and DDT indicates that it affects developing

organisms differently than it does mature organisms. Furthermore, the functional deficits in animals and humans as a result of exposure in the womb can occur at much lower concentrations than that required to illicit similar changes in adults(18,19,20). And most important, only one exposure, called a "hit", at a critical window of time during sexual differentiation can change the course of sexual development of the exposed individual(18,19,20,21).

It is during differentiation that construction of the vital physiological systems and programming of the pituitary/hypothalamic region of the brain takes place. It is also at this time that endocrine disruptors may be the most threatening, leading to endocrine, immune, and nervous systems that are architecturally unsound and hypothalmi that do not respond to normal hormonal and neurotransmitter messages in the usual manner throughout life(20). The insidious nature of these effects makes the induced modifications difficult to discern, since in most cases, they are expressed in the offspring of the individuals who were exposed, not the exposed parents.

The endocrine system holds the key to fertility. For some sensitive populations the message is clear, avoidance and prevention are the only options for survival. Meanwhile, as decision makers wait for tolerance levels, dose-response curves, threshold levels, and unequivocal cause-effect linkages in order to regulate on a chemical-by-chemical basis, evidence that more and more synthetic chemicals are being passed from mother to offspring

continues to surface(21,22). Top predator, long-lived wildlife populations are suffering declines. Evidence of human damage as the result of generational transfer of synthetic chemicals is accumulating.

**EXTRAPOLATING TO HUMANS**

There is evidence that many manmade chemicals can invade the pristine environment of the womb(23,24). Defying the paradigm that the placenta is impenetrable to exogenous compounds, the chemicals readily cross the placenta and brain barrier as they are passed from the mother to her developing baby. In addition, in the case of estrogen-like compounds, if they do not bind to the estrogen-binding protein in human maternal blood that protects the fetus from a large part of maternally-produced estrogen during gestation(25), their toxicity will be enhanced(8).

Using the laboratory animal as a model, the disruptive effects associated with exposure to developmental toxicants in the womb can range from mild to extreme, reflecting gradations of loss of potential. The effects are not necessarily expressed as a clinically relevant disease state. Furthermore, in many cases the effects are irreversible(8). There are an infinite number of "windows of time" during embryonic and the early postnatal period when disruption can take place, each leading to potentially different changes in an individual's course of development and behavior. Response to exposure is unpredictable because the process of development is so delicate and complex. Consequently,

a simple, standardized descriptor of damage can never be generated. For long-lived humans, the effects may never be traced to a specific exposure event because the effects can be expressed twenty years or more later -- the disconnect between exposure and effect is too great. Ultimately, exposure of this nature leads to loss of potential at the individual level. But, at the population level, the effects could have vast social and economic impacts(26).

The full impact of exposure to chemicals on humans may just be coming to light. Because the effects are not expressed as physical disfigurement at birth, they do not appear in public health birth records. They often require a generation or more before they are recognized. For example, loss of fertility that includes reduced sperm count associated with exposure to "estrogens"(27), shortened penises at puberty associated with exposure to PCBs and furans(28), cognitive and motor loss associated with exposure to PCBs(29), and aberrant immune responses associated with exposure to diethylstilbestrol(30,31) have all been documented in humans as a result of their exposure in the womb. None of the above was predictable at birth using current clinical examination procedures. And none is described as a single disease or syndrome associated with exposure to one, or a class, of chemicals.

Human studies should take into consideration the functional deficits reported in wildlife resulting from transgenerational exposure. Likewise, consideration should be given to the extent of constrained potential in our children that includes behavioral, cognitive, social, immunological, and endocrinological endpoints.

This will be a daunting task because of the widespread use and distribution of pesticides and industrial chemicals.

**DISCUSSION**

A veneer of long-lived, manmade chemicals now covers the earth from the Arctic to the Antarctic(32). Concentrations of these chemicals that include a number of organochlorine pesticides, are now at levels associated with population declines of marine, freshwater, and terrestrial animals and with functional deficits in human offspring(33). It is impossible to predict the effect of the addition of a single new chemical to this veneer let alone the addition of several hundred or more new chemicals a year that are introduced into commerce. It is doubtful that unequivocal cause and effect relationships will ever be made for the wildlife population declines and the human loss of potential mentioned above because so many chemicals are involved, many of which have never been identified analytically.

Unlike many of the developmental toxicants that are unintentionally produced, pesticides are produced and released to the environment intentionally. This provides opportunities to control further release of pesticidal compounds currently in use until proven safe and to prevent the release of new substitutes that may pose similar or greater threats. However, under the current regulatory system in order to accomplish this, a case has to be made that the chemicals are, indeed, harmful. This can only be accomplished with quantitative evidence of damage.

Unfortunately, the research agenda today in the US is not organized to support science of this nature. Most of the current wildlife toxicology research comes as a result of serendipitous observations by scientists engaged in unrelated fields of studies or from reactive science to severe damage in areas heavily contaminated. Most of the human studies have also been in reaction to concern over high-dose exposure.

Currently no governmental institution is dedicated solely to promoting innovative, multidisciplinary research on transgenerationally-transmitted loss of function. This will require multi-level (gene to ecosystem) research, that addresses real-world pollutions problems. Real-life exposure and effect studies should be encouraged using free-ranging wildlife as models for human exposure and effects. This will require extensive activities in the field, followed in the laboratory with replication of the damage found in the field, and should lead to the determination of the most sensitive endpoint(s) (the lower-limits of effect) on offspring using a multigenerational model.

To assure that the research agenda is modernized to meet society's current needs, a review process must be created 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 multi-disciplinary review process separate from the current practice in use in federal institutions today.

In addition to the institutionalization of ecotoxicological

research, there are other research needs for:

(1) the development of inexpensive, short-term screening techniques to test new and old products for endocrine, nervous, and immune system disruptive capacity.

(2) the acceleration of testing of banned and restricted products that still pose a threat to humans and wildlife because of their persistence and presence in human tissue.

(3) industry to test all new products, their metabolites, intermediates, and by-products for: (1) multigenerational immune, endocrine, reproductive, and nervous system effects in at least three animal species and (2) their environmental fate in all media.

(4) industry to provide the chemical analytical protocol to monitor its new products in the environment after they have been released.

In light of the new evidence about the endocrinological effects of PCBs, dioxins, furans, DDT and its analogs, and a growing list of pesticides and other chemicals used in commerce, it is prudent that society makes a concerted effort to reexamine the endocrinological effects of (1) all pesticides in use, (2) any new pesticides that will come on the market, and (3) those that have been banned and restricted but still persist in the environment. Many of the latter chemicals have proved to be very persistent and are still present in the US environment at dangerous levels(34,35). In addition, their use has not been discontinued overseas, and in some instances are being used at

greater intensity overseas than ever used in the US.

**CONCLUSION**

Institutions will continue to fail to translate into policy the impacts of developmental toxicants on wildlife and humans if they remain locked into the current mode of testing and continue to function in a reactionary manner. Testing must be broadened to include real-world experiences for both wildlife and humans. Until institutions shift into a preventive mode and incorporate these forensic studies in their agendas, little will change. It is also imperative that the cumulative results of the new testing be systematically reviewed and synthesized. And most important, the results of these syntheses must become an accepted component of the decision-making process.

ACKNOWLEDGEMENT: I am indebted to Rich Liroff and Michael Gilbertson for the time and consideration they gave to this paper.

Table 1. Environmental effects reported in wildlife on the development of hormonally responsive tissue.

| |
|---|
| DECREASES |
| Embryo hatchability(36) |
| Embryo viability(37) |
| Chick survivorship(38) |
| Fry survivorship(39) |
| Egg size and numbers(40) |
| Numbers of animals reaching sexual maturity(14,41) |
| Production of thyroid hormones(12,41,42) |
| Production of estrogen(43) |
| Production of testosterone(44,45) |
| Production of retinols(12) |
| Immune-competency(46) |
| INCREASES |
| Size of thyroid(47) |
| Size of liver(17) |
| Liver enzyme induction(17) |
| Highly carboxylated porphyrins(48) |
| Numbers of animals exhibiting sex reversal(6,14,49,50) |
| Spontaneous abortions(51) |
| Hermaphroditism(14,52) |
| Sex-linked birth defects(53) |

Assymetrical brains(54)

Assymetrical skulls(55)

Unusual behavior(11,12,13)

## REFERENCES


1. U.S. Congress, Office of Technology Assessment. Researching Health Risks. OTA-BBS-571. November, 1993. 44p.

2. Carson R. Silent spring. Boston, MA:Houghton Mifflin Co(1962).

3. Special issue: International Joint Commission workshop on cause-effect linkages. Jrl Toxicol Environ Health 1991;33(4).

4. Colborn T, Davidson A, Green SN, Hodge RA, Jackson CI, Liroff RA. Great Lakes, great legacy? Washington, DC:Conservation Foundation (1990).

5. Colborn T, Clement C. eds. Chapter I in Chemically-induced alterations in sexual and functional development: the wildlife/human connection. Princeton, NJ:Princeton Scientific Publishing (1992).

6. Colborn T, Clement C. eds. Chemically-Induced Alterations in Sexual and Functional Development: The Willdife/Human Connection. Princeton, NJ:Princeton Scientific Publishing (1992).

7. Colborn T, vomSaal F, Soto A. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. EHP 101(5):378-384(1993).

8. Clement C, Colborn T. Herbicides and fungicides: a perspective on potential human exposure. In:Chemically-induced alterations in sexual and functional development: the wildlife/human connection (Colborn T, Clement C, eds). Princeton, NJ:Princeton Scientific Publishing, 1992;347-364.

9. Burlington H, Lindeman VF. Effect of DDT on testes and secondary sex characters of white leghorn cockerels. Proc Soc Exp Biol Med 74:48-51(1950).

10. Shugart, G. Frequency and distribution of polygony in Great Lakes herring gulls in 1978. Condor 82:426-429(1980).

11. Fox G. Epidemiological and pathological evidence of contaminant-induced alterations in sexual development in free-living wildlife. In: Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection (Colborn T, Clement C, eds). Princeton, NJ:Princeton Scientific Publishing. 1992;147-158.

12. Fry DM, Toone CK. DDT-induced feminization of gull embryos. Science 231:919-924(1981).

13. Fry D, Toone C, Speich S, Peard R. Sex ratio skew in breeding patterns of gulls: demographic and toxicological considerations. Studies Avian Biol10:26-43(1987).

14. Guillette L. Written testimony for Congressional Hearing before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, sponsored by Congressman Henry Waxman, October 21, 1993.

15. 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.

16. Bern HA. The fragile fetus. In:Chemically-induced alterations in sexual and functional development: the wildlife/human connection (Colborn T, Clement C, eds). Princeton, NJ:Princeton Scientific Publishing, 1992;9-15.

17. Mori T, Nagasawa H. (eds) Toxicity of hormones in perinatal life. Boca Raton,FL:CRC Press, 1988.

18. Mably TA, Moore RW, Peterson RE. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin: 1. Effects on androgenic status. Toxicol Appl Pharmacol 114:97-107(1992).

19. Mably TA, Moore RW, Goy RW, Peterson RE. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin: 2. Effect on sexual behavior and the regulation of luteinizing hormone secretion in adulthood. Toxicol Appl Pharmacol 114:108-117(1992).

20. Mably TA, Bjerke DL, Moore RW, Gendron-Fitzpatrick A, Peterson RE. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin: 3. Effects on spermatogenesis and reproductive capability. Toxicol Appl Pharmacol 114:118-126(1992).

21. Thomas KB, Colborn TE. 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.

22. Jensen AA, Slorach SA. eds. Chemical contaminants in human milk. Boston,MA:CRC Press(1991).

23. Saxena MC, Siddiqui MKJ, Agarwal V, Kuuty D. A comparison of organochlorine insecticide contents in specimens of maternal blood, placenta, and umbilical cord-blood from stillborn and live-born cases. J Toxicol Environ Health 11:71-19(1983).

24. Skaare JU, Tuveng JM, Sande HA. Organochlorine pesticides and polychlorinated biphenyls accumulating in maternal adipose tissue, blood, milk, and cord blood from mothers and infants living in Norway. Arch Environ Contam Toxicol 17:55-63(1988).

25. Sheehan DM, Young M. Diethylstilbestrol and estradiol binding to serum albumin and pregnancy plasma of rat and human. Endocirnology 104:1442-1446(1979).

26. Colborn T. Nontraditional evaluation of risk from fish contaminants. In: Proceedings of a symposium on issues in seafood safety (ed. Ahmed FE) Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, 1991:95-155.

27. Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. Br Med J 304:609-613(1992).

28. 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:(in press).

29. Jacobson JL, Jacobson SW, Humphrey HEB. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J Pediatr 11638-45(1990).

30. 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;289-294.

31. Blair PB, Noller KL, Turiel 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). Princeton, NJ:Princeton Scientific Publishing, 1992;283-288.

32. Colborn T. Global implications of Great Lakes wildlife research. Int Environ Affairs 3(1):3-25(1991).

33. Colborn T. The wildlife/human connection: modernizing risk decisions. EHP (in press).

34. Anthony RG, Garrett M, Schuler C. Environmental contaminants in bald eagles in the Columbia River estuary. J Wildl Manage 57(1):10-18(1993).

35. Jarman WM, Burns SA, Chang RR, Stephens RD, Norstrom RJ, Simon M, Linthicum J. Determination of PCDDS, PCDFS, and PCBS in Califorina pergrine falcons (FALCO PEREGRINUS) and their eggs. Environ Toxicol Chem 12:105-114(1993).

36. 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).

37. Tillit DE, Ankley GT, Giesy 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 mortality in double-crested cormorants from the Great Lakes. Environ Tox Chem 11:1281-1288(1992).

38. Kubiak T, Harris H, Smith L, Schwartz T, Stalling D, Trick J, Sileo L, Docherty 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).

39. 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). New Jersey:Princeton Scientific Publishing, 1992:195-202.

40. McMaster ME, Portt CB, Munkittrick 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).

41. 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). New Jersey:Princeton Scientific Publishing, 1992:129-146.

42. Leatherland JF, Lin L, Down NE, Donaldson EM. Thyroid hormone content of eggs and early developmental stages of three stocks of goitred 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).

43. Munkittrick 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 (Catostomus commersoni) population. Can J Fish Aquat Sci 48:1371-1380(1991).

44. Munkittrick KR, Van Der Kraak GJ, McMaster ME, Portt CB. Response of hepatic MFO activity and plasma sex steroids to secondary treatmant of bleached kraft pulp mill effluent and mill

shutdown. Env Toxicol Chem 11:1427-1439(1992).

45. Subramanian A, Tanabe S, Tatsukawa R, Saito S, Mirgazaki N. Reductions in the testosterone levels by PCBs and DDE in Dall's porpoises of northwestern North Pacific. Marine Pollut Bull 18(12):643-646(1987).

46. Martineau D, Lagace A, Beland P, Higgins R, Armstrong D, Shugart LR. Pathology of stranded beluga whales (Delphinapterus leucas) from the St. Lawrence Estuary, Quebec, Canada, J Comp Path 93(3):287-311(1988).

47. Moccia 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).

48. Fox G, Kennedy S, Norstrom R, Wigfield D. Porphyria in herring gulls: a biochemical response to chemical contamination of Great Lakes food chains. Environ Toxicol Chem 7:831-839(1988).

49. Gibbs PE, Pascoe PL, Burt GR. Sex change in the female dog-whelk, Nucella lapillus, induced by tributyltin from antifouling paints. J Mar Biol Assoc UK 68:715-731(1988).

50. Davis WP, Bortone SA. Effects of kraft mill effluent on the sexuality of fishes: an environmental early warning? In: Chemically induced alterations in sexual and functional development: the wildlife/human connection (Colborn T, Clement C eds). New Jersey:Princeton Scientific Publishing, 1992;113-128.

51. Reijnders PJH. Reproductive failure in common seals feeding on fish from polluted coastal waters. Nature 324:456-457(1986).

52. DeGuise S, Lagace A, Beland P. Hermaphroditism in a beluga whale. J Wildlife Dis (in press).

53. Personal communication: Fry M, UC, Davis, all crossed bill double-crested cormorants examined were phenotypic females (n=>100); Kubiak, T, USFWS, Washington, DC, all crossed bill bald eagle chicks discovered in 1993 were females (n=3).

54. Henshel DS, Cheng KM, Norstrom R, Whitehead P, Steeves JD. Morphometric and histological changes in brains of great blue heron hatchlings exposed to PCDDs: preliminary analysis. In: Environmental toxicology and risk assessment: aquatic, plant, terrestrial symposium. ATSDR in press.

55. Zakharov VM, Yablokov AV. Skull asymmetry in the baltic grey seal: effects of environmental pollution. Ambio 19(5):266-269(1990).