Consensus Statement: Atlantic Coast Contaminants Workshop 2000

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In humans and wildlife, there are known associations between exposure to endocrine-disrupting chemicals and effects on human and ecosystem health. However, causative linkages between the role of these chemicals and observed endocrine-related abnormalities are virtually nonexistent. Three exceptions exist in humans: *a*) associations between high polychlorinated biphenyl (PCB) and polychlorinated dibenzodioxin and dibenzofuran (PCDD/PCDF) exposure *in utero* and possibly via breast-feeding, and neurobehavioral deficits; *b*) increasing support for an association between breast cancer risk and exposure to PCB and/or DDTs; and *c*) one study demonstrating an association between dieldrin exposure and breast cancer risk and mortality. In wildlife species, however, strong evidence in laboratory, field studies, and semi-field studies with harbor seals from the Dutch Wadden Sea have shown correlations between contaminant exposure and endocrine-related effects such as developmental-, reproductive-, and immune-associated toxicities. In general, exposure of marine mammals to persistent chlorinated hydrocarbon contaminants and their metabolites has been implicated as a causative factor in sterility, growth retardation, perturbation of immunologic function, and reproductive abnormalities. The reported reproductive abnormalities range from subtle to permanent, such as disturbed sex differentiation (i.e., feminized or masculinized sex organs and changes in sexual or other behaviors). Effects have been observed in mammals, birds, reptiles, fish, and molluscs from Europe, North America, and other continents. Well-known examples include DDE-associated thinning of bird egg shells, organotin-induced imposex in marine snails from various marine waters experiencing heavy shipping traffic, contaminant-linked effects on reproductive organs in fish species from rivers in the United Kingdom, and pesticide-associated effects on sex organ development and function in American alligators from Lake Apopka in Florida. Other examples include *a*) the linkage between exposure to high PCB and methylsulfone ($MeSO_2$)-PCB and $MeSO_2$-DDE concentration and a disease complex characterized by adrenocortical hyperplasia in Baltic ringed seals, and *b*) chronic and reproductive toxicities observed for female mink fed a diet containing a mixture of environmentally relevant $MeSO_2$-PCBs and $MeSO_2$-DDE. Correlations have even been observed in contaminant-exposed species such as polar bear and greater scaup ducks, from geographically remote Arctic regions.

In light of this knowledge, 22 wildlife and human health experts gathered at the Atlantic Coast Contaminants Workshop in Bar Harbor, Maine, to discuss the topic of "Endocrine Disruptors in the Marine Environment: Impacts on Marine Wildlife and Human Health." Participants were expected to reach some conclusions regarding the nature, magnitude, and scope of the problem in the north Atlantic ecosystem.

Participants reported on potential endocrine-related effects and impacts in wildlife and humans resulting from contaminant- and noncontaminant-related factors. Natural ecologic influences such as marine mammal strandings were discussed. Methods and biomarkers of endocrine-related impacts were presented including those based on inducible genes; clinical parameters and population monitoring of bottlenose dolphins; probable risk assessment of reproductive effects; comparative biochemistry of species-dependent, Ah receptor-based assays; and contaminant interaction and mechanisms of thyroid hormone-dependent processes. Possible contaminant-mediated impacts on alterations in population health, reproduction, steroid hormone homeostasis and/or immunologic alterations were outlined for cetaceans from the Atlantic Ocean; native Inuit peoples from northern Quebec, Canada; bald eagles from the northeastern United States; St. Lawrence beluga whales; polar bears from Svalbard, Norway; scaup ducks from Alaska or Canada wintering in the northeastern United States; and a variety of birds, fish, and aquatic mammals from Arctic, Atlantic, and other marine ecosystems. The utility of humans and aquatic wildlife as sentinels and surrogates of endocrine-related effects resulting from contaminant exposure was also discussed.

Discussions and presentations emphasized the involvement of bioaccumulating, primary organochlorine contaminants such as PCBs, DDTs, and other pesticides, as well as exposure to metals and metal-containing organics such as methylmercury and organotins. Persistent or retained metabolites of xenobiotics can mediate, at least in part, the effects linked to the primary compounds. Hydroxylated- and $MeSO_2$-PCB metabolites were discussed as second level contaminants that have demonstrated endocrine activity *in vitro* and *in vivo* via sex hormone receptor interactions, hormone transport protein [e.g., thyroid transport protein (TTR)], estrogen-stimulated cellular gene expression, and/or effects on enzyme systems involved in hormone biosynthesis or metabolism. The brominated flame retardants (polybrominated diphenyl ethers and their hydroxylated analogues) were shown to interact strongly with TTR and on estrogen receptor or estrogen-responsive gene expression. Exogenous compounds that have been investigated for endocrine-related activity include bioaccumulating and nonbioaccumulating contaminants, but represent only a fraction of xenobiotics with potential endocrine-disrupting properties

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that are present in the environment. This indicates a need for further research to identify what are likely hundreds or perhaps thousands of as yet unidentified endocrine-disrupting xenobiotics in biota. Further, we must obtain actual exposure data for these compounds in human and wildlife.

The participants of the workshop reached the following consensus.

At this point in time, it is clear that a connection exists between human and wildlife exposure to a variety of environmental contaminants, and effects on endocrine systems and/or processes that are endocrine dependent. One must also consider persistent or retained metabolites of xenobiotics mediating, at least in part, the effects linked to the primary compounds. Thus, the contaminant exposure–endocrine system linkage is no longer a hypothesis, but constitutes a real health hazard to wildlife and humans. Numerous contaminant–effect associations have been reported and are strongly suggestive of possible impacts. Demonstrating that a compound is indeed endocrine disruptive is however contingent on the contaminant(s), exposure level, individual genetic sensitivity, species-dependent mechanism of action, and selection of relevant endocrine end point(s) to be measured.

A difference between human toxicology and ecotoxicology is the concern with individuals versus populations, respectively. Food is a major exposure route for both wildlife and humans. However, human exposure is contrasted by the realities of modern society, that is, consumer products, artificial living environments, and urban air pollution. In the context of wildlife and ecotoxicologic research, the study of endocrine-disruption effects is restricted by the difficulty in obtaining a sample size that is truly representative of the population. Thus, it must be considered relevant to regard individual members as representative of the population or at least part of the population. Regardless, subtle effects in individuals can be viewed as significant and as indicators of potential worst-case scenarios. The ability and adaptability of a species to deal with environmental- and/or contaminant-mediated stressors will define the resiliency and robustness of a population or subpopulation.

To date, impacts on endocrine systems that are strongly associated with contaminant exposure have been reported for geographically localized populations. However, environmental contamination is global, although exposure levels in biota may not necessarily be high enough to evoke acute and observable effects. Rather, the impacts are most likely of a subtle, chronic, and perhaps insidious nature. Nevertheless, even seemingly minor perturbations in an endocrine-associated parameter can potentially set into motion a series of biological events, which could have more widespread ecotoxicologic impacts. There are other known environmental stressors, including the intrinsic factors such as sex, age, nutritive and health condition, and reproductive status, which can be difficult to differentiate from subtle contaminant-linked effects and extrinsic factors such as habitat quality and stochastic environmental events. Therefore, it is likely that subtle population impacts have to be viewed holistically as the summation of low-level contaminant exposure and ecologic factors.

A major effort to incorporate interdisciplinary research is an absolute necessity to understand the complex issue of endocrine disruption. A truly integrated approach will involve concerted interaction and cooperation between environmental researchers from diverse scientific disciplines. Although experimental, wildlife, and epidemiologic approaches each have their strengths and weaknesses, the complementarity of those data will greatly strengthen the weight of evidence. In doing so, the scientific community will be more effective in convincing people and regulatory bodies of the importance of the endocrine-disruption issue to society.

Major gaps and deficiencies remain in our understanding of endocrine disruption (in no specific order):

- Although in some cases, "old" chemicals (such as PCBs in marine mammals) are still relevant, metabolites and new compounds need to be better addressed. For all chemicals, precise and comprehensive (congener-specific) analytical chemistry will be required to fully assess the distribution of the chemicals involved. Also, extensive sampling will be needed to better characterize exposure (we cannot guess exposure).
- More forensic analysis of the environment is needed in order to discover and characterize exposure to new contaminants in a timely manner.
- Exposure at early stages of life (development) is important because it represents the most sensitive period for several effects. Nevertheless, critical life stages such as puberty and aging can be highly relevant for effects on reproduction, the immune system, or life-altering behavior.
- Classical lipid-based contaminants that bioaccumulate have thus far been a major focus. Nevertheless, other contaminants that are not soluble in fat and that do not bioaccumulate should not be forgotten because they may have equal importance.
- Lack of standardization in presentation of the chemical analysis data is a major obstacle in the interpretation and comparison of data from different studies.
- Although there are several systems that can demonstrate effects at the molecular and cellular level, there should be efforts at demonstrating repercussions at the individual and population level.
- Whereas attention has been focused on the health of the current population and directly exposed individuals, more focus should be placed on subtle contaminant-linked effects that may nevertheless have devastating consequences in offspring.
- Although receptor-based assays can be very useful, it is imperative to recognize that endocrine-disruptive effects can also be mediated through interactions at different levels. It will be important to design assays that will be directed toward understanding the mechanism(s) involved, which will further help in the interpretation of the results.
- It is important to recognize that genetic variability may affect the susceptibility of individuals or populations to the effects of pollutants.
- Understanding limitations of methods will be critical in the choice of complementary methods to confirm another method's findings and adequate interpretation of results.
- There is a general lack of relevant physiologic "normal" range data for wildlife, making the determination of abnormal findings difficult.
- Exposure to high and low doses of contaminants may have different effects. It is important to use ecologically relevant ranges of doses for each species studied. Special consideration must be given to possible low-dose threshold levels for subtle effects in young animals of every species.
- Multichemical interactions of ecologically relevant mixtures (at relevant concentrations) for a species are required because chemical mixtures can have an effect different from the sum of the effects of each component of the mixture.
- Highly mobile populations such as migratory mammals, birds, fish, or humans may respond to adverse habitat conditions by shifts in seasonal range that can alter levels of exposure.
- Lack of data does not mean lack of effects, nor does it mean effects; it means just lack of data.
- Addressing the concept of subtle and chronic endocrine effects may prove to be the greatest challenge. Many potential modes of action and pathways leading to endocrine disruption have yet to be discovered and researched. Coupled with the growing list of xenobiotics that are endocrine active, we presently sit at the threshold of understanding what we define as "endocrine disruption."

This consensus statement reflects the professional wisdom of the scientists at the working sessions and not necessarily the institutions or agencies in which they are employed.