STATEMENT FROM THE WORK SESSION ON

CHEMICALLY-INDUCED ALTERATIONS IN SEXUAL DEVELOPMENT: THE WILDLIFE/HUMAN CONNECTION

THE PROBLEM

Many compounds introduced into the environment by human activity are capable of disrupting the endocrine system of animals, including fish, wildlife, and humans. The consequences of such disruption can be profound because of the crucial role hormones play in controlling development. Because of the increasing and pervasive contamination of the environment by compounds capable of such activity, a multidisciplinary group of experts gathered in retreat at Wingspread, Racine, Wisconsin, 26-28 July 1991 to assess what is known about the issue. Participants included experts in the fields of anthropology, ecology, comparative endocrinology, histopathology, immunology, mammalogy, medicine, law, psychiatry, psychoneuroendocrinology, reproductive physiology, toxicology, wildlife management, tumor biology, and zoology.

The purposes of the meeting were:

1. to integrate and evaluate findings from the diverse research disciplines concerning the magnitude of the problem of endocrine disruptors in the environment;
2. to identify the conclusions that can be drawn with confidence from existing data; and
3. to establish a research agenda that would clarify uncertainties remaining in the field.

CONSENSUS STATEMENT

The following consensus was reached by participants at the workshop.

1. *We are certain of the following:*

    - A large number of man-made chemicals that have been released into the environment, as well as a few natural ones, have the potential to disrupt the endocrine system of animals, including humans. Among these are the persistent, bioaccumulative, organohalogen compounds that include some pesticides (fungicides, herbicides, and insecticides) and industrial chemicals, other synthetic products, and some metals.[1]

[1]Chemicals known to disrupt the endocrine system include: DDT and its degradation products, DEHP (di(2-ethylhexyl)phthalate), dicofol, HCB (hexachlorobenzene), kelthane, kepone, lindane and other hexachlorocyclohexane congeners, methoxychlor, octachlorostyrene, synthetic pyrethroids, triazine herbicides, EBDC fungicides, certain PCB congeners, 2,3,7,8-TCDD and other dioxins, 2,3,7,8-TCDF and

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- Many wildlife populations are already affected by these compounds. The impacts include thyroid dysfunction in birds and fish; decreased fertility in birds, fish, shellfish, and mammals; decreased hatching success in birds, fish, and turtles; gross birth deformities in birds, fish, and turtles; metabolic abnormalities in birds, fish, and mammals; behavioral abnormalities in birds; demasculinization and feminization of male fish, birds and mammals; defeminization and masculinization of female fish and birds; and compromised immune systems in birds and mammals.

- The patterns of effects vary among species and among compounds. Four general points can nonetheless be made: (1) the chemicals of concern may have entirely different effects on the embryo, fetus, or perinatal organism than on the adult; (2) the effects are most often manifested in offspring, not in the exposed parent; (3) the timing of exposure in the developing organism is crucial in determining its character and future potential; and (4) although critical exposure occurs during embryonic development, obvious manifestations may not occur until maturity.

- Laboratory studies corroborate the abnormal sexual development observed in the field and provide biological mechanisms to explain the observations in wildlife.

- Humans have been affected by compounds of this nature, too. The effects of DES (diethylstilbestrol), a synthetic therapeutic agent, like many of the compounds mentioned above, are estrogenic. Daughters born to mothers who took DES now suffer increased rates of vaginal clear cell adenocarcinoma, various genital tract abnormalities, abnormal pregnancies, and some changes in immune responses. Both sons and daughters exposed *in utero* experience congenital anomalies of their reproductive system and reduced fertility. The effects seen in *in utero* DES-exposed humans parallel those found in contaminated wildlife and laboratory animals, suggesting that humans may be at risk to the same environmental hazards as wildlife.

2. *We estimate with confidence that:*

   - Some of the developmental impairments reported in humans today are seen in adult offspring of parents exposed to synthetic hormone

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other furans, cadmium, lead, mercury, tributyltin and other organo-tin compounds, alkyl phenols (non-biodegradable detergents and anti-oxidants present in modified polystyrene and PVCs), styrene dimers and trimers, soy products, and laboratory animal and pet food products.

disruptors (agonists and antagonists) released in the environment. The concentrations of a number of synthetic sex hormone agonists and antagonists measured in the US human population today are well within the range and dosages at which effects are seen in wildlife populations. In fact, experimental results are being seen at the low end of current environmental concentrations.

- Unless the environmental load of synthetic hormone disruptors is abated and controlled, large scale dysfunction at the population level is possible. The scope and potential hazard to wildlife and humans are great because of the probability of repeated and/or constant exposure to numerous synthetic chemicals that are known to be endocrine disruptors.

- As attention is focused on this problem, more parallels in wildlife, laboratory, and human research will be revealed.

3. *Current models predict that:*

   - The mechanisms by which these compounds have their impact vary, but they share the general properties of (1) mimicking the effects of natural hormones by recognizing their binding sites; (2) antagonizing the effect of these hormones by blocking their interaction with their physiological binding sites; (3) reacting directly and indirectly with the hormone in question; (4) by altering the natural pattern of synthesis of hormones; or (5) altering hormone receptor levels.

   - Both exogenous (external source) and endogenous (internal source) androgens (male hormones) and estrogens (female hormones) can alter the development of brain function.

   - Any perturbation of the endocrine system of a developing organism may alter the development of that organism: typically these effects are irreversible. For example, many sex-related characteristics are determined hormonally during a window of time in the early stages of development and can be influenced by small changes in hormone balance. Evidence suggests that sex-related characteristics, once imprinted, may be irreversible.

   - Reproductive effects reported in wildlife should be of concern to humans dependent upon the same resources, e.g., contaminated fish. Food fish is a major pathway of exposure for birds. The avian (bird) model for organochlorine endocrine disruption is the best described to date. It also provides support for the wildlife/human connection because of similarities in the development of the avian and mammalian endocrine systems.

4. *There are many uncertainties in our predictions because:*

   - The nature and extent of the effects of exposure on humans are not well established. Information is limited concerning the disposition of these contaminants within humans, especially data on concentrations of contaminants in embryos. This is compounded by the lack of measurable endpoints (biologic markers of exposure and effect) and the lack of multi-generational exposure studies that simulate ambient concentrations.

   - While there are adequate quantitative data concerning reduction in reproductive success in wildlife, data are less robust concerning changes in behavior. The evidence, however, is sufficient to call for immediate efforts to fill these knowledge gaps.

   - The potencies of many synthetic estrogenic compounds relative to natural estrogens have not been established. This is important because contemporary blood concentrations of some of the compounds of concern exceed those of internally produced estrogens.

5. *Our judgment is that:*

   - Testing of products for regulatory purposes should be broadened to include hormonal activity *in vivo*. There is no substitute for animal studies for this aspect of testing.

   - Screening assays for androgenicity and estrogenicity are available for those compounds that have direct hormonal effects. Regulations should require screening all new products and by-products for hormonal activity. If the material tests positive, further testing for functional teratogenicity (loss of function rather than obvious gross birth defects) using multigenerational studies should be required. This should apply to all persistent, bioaccumulative products released in the past as well.

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

   - A more comprehensive inventory of these compounds is needed as they move through commerce and are eventually released to the environment. This information must be made more accessible. Information such as this affords the opportunity to reduce exposure through containment and manipulation of food chains. Rather than

separately regulating contaminants in water, air, and land, regulatory agencies should focus on the ecosystem as a whole.

- Banning the production and use of persistent chemicals has not solved the exposure problem. New approaches are needed to reduce exposure to synthetic chemicals already in the environment and prevent the release of new products with similar characteristics.

- Impacts on wildlife and laboratory animals as a result of exposure to these contaminants are of such a profound and insidious nature that a major research initiative on humans must be undertaken.

- The scientific and public health communities' general lack of awareness concerning the presence of hormonally active environmental chemicals, functional teratogenicity, and the concept of transgenerational exposure must be addressed. Because functional deficits are not visible at birth and may not be fully manifested until adulthood, they are often missed by physicians, parents, and the regulatory community, and the causal agent is never identified.

6. *To improve our predictive capability:*

- More basic research in the field of developmental biology of hormonally responsive organs is needed. For example, the amount of specific endogenous hormones required to evoke a normal response must be established. Specific biologic markers of normal development per species, organ, and stage of development are needed. With this information, levels that elicit pathological changes can be established.

- Integrated cooperative research is needed to develop both wildlife and laboratory models for extrapolating risks to humans.

- The selection of a sentinel species at each trophic level in an ecosystem is needed for observing functional deficits, while at the same time describing the dynamics of a compound moving through the system.

- Measurable endpoints (biologic markers) as a result of exposure to exogenous endocrine disruptors are needed that include a range of effects at the molecular, cellular, organismal, and population levels. Molecular and cellular markers are important for the early monitoring of dysfunction. Normal levels and patterns of isoenzymes and hormones should be established.

- In mammals, exposure assessments are needed based on body burdens of a chemical that describe the concentration of a chemical

in an egg (ovum) which can be extrapolated to a dose of the chemical to the embryo, fetus, newborn, and adult. Hazard evaluations are needed that repeat in the laboratory what is being seen in the field. Subsequently, a gradient of doses for particular responses must be determined in the laboratory and then compared with exposure levels in wildlife populations.

- More descriptive field research is needed to explain the annual influx to areas of known pollution of migratory species that appear to maintain stable populations in spite of the relative vulnerability of their offspring.

- A reevaluation of the *in utero* DES-exposed population is required for a number of reasons. First, because the unregulated, large-volume releases of synthetic chemicals coincide with the use of DES, the results of the original DES studies may have been confounded by widespread exposure to other synthetic endocrine disruptors. Second, exposure to a hormone during fetal life may elevate responsiveness to the hormone during later life. As a result, the first wave of individuals exposed to DES *in utero* is just reaching the age where various cancers (vaginal, endometrial, breast, and prostatic) may start appearing if the individuals are at a greater risk because of perinatal exposure to estrogen-like compounds. A threshold for DES adverse effects is needed. Even the lowest recorded dose has given rise to vaginal adenocarcinoma. DES exposure of fetal humans may provide the most-severe-effect model in the investigation of the less potent effects from environmental estrogens. Thus, the biological endpoints determined in *in utero* DES-exposed offspring will lead the investigation in humans following possible ambient exposures.

- The effects of endocrine disruptors on longer-lived humans may not be as easily discerned as in shorter-lived laboratory or wildlife species. Therefore, early detection methods are needed to determine if human reproductive capability is declining. This is important from an individual level, as well as at the population level, because infertility is a subject of great concern and has psychological and economic impacts. Methods are now available to determine fertility rates in humans. New methods should involve more use of liver-enzyme-system activity screening, sperm counts, analyses of developmental abnormalities, and examination of histopathological lesions. These should be accompanied by more and better biomarkers of social and behavioral development, the use of multigenerational histories of individuals and their progeny, and congener-specific chemical analyses of reproductive tissues and products, including breast milk.

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