TEDX
The Endocrine Disruption Exchange

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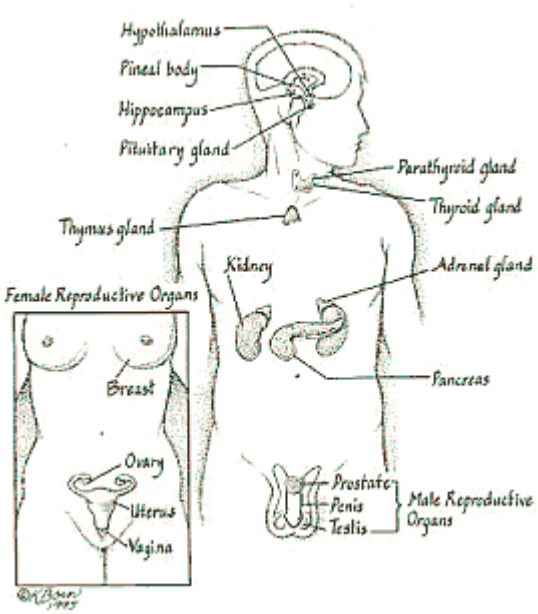
Written Statement of
Theo Colborn, President, TEDX

Committee on Natural Resources
Subcommittee on Insular Affairs, Oceans. And Wildlife
"Overdose: How Drugs and Chemicals in Water and the Environment are Harming Fish and Wildlife"

June 9, 2009

My name is Theo Colborn. I am an environmental health analyst, President of TEDX, a 501(c)(3) organization located in Paonia Colorado, and a Professor Emeritus at the University of Florida, Gainesville. I have a BS in pharmacy from Rutgers University, New Jersey, an MA in freshwater ecology from Western State College, Gunnison, Colorado, and a PhD in zoology from the University of Wisconsin, Madison, Wisconsin, with distributed minors in epidemiology, toxicology, and water chemistry. My field and laboratory research for the graduate level degrees involved tracking the mobilization of low levels of toxic trace metals in high altitude streams in Colorado using the exoskeletons of insects that live in water. In 1985 I moved to Washington, DC on a Fellowship from the US Congress's Office of Technology Assessment, and later established and ran the Wildlife and Contaminants Program at World Wildlife fund until 2003. I have served on the US Environmental Protection Agency (EPA) Science Advisory Board and several EPA panels, the US and Canadian State Departments' International Joint Commission's Ecosystem Health Committee for 19 years, and advised Environment Canada, Health Canada, the US Fish and Wildlife Service, the US Department of the Interior, the Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry, and similar government agencies in Europe, the United Kingdom, and Japan. I have published in scientific journals and books on the effects of low level and/or ambient exposure to toxic chemicals that interfere with the endocrine system, which has initiated action at the state, national, and international levels to improve the protocols for testing chemicals when determining their safety. In 2002, I returned home to Paonia, Colorado where I established TEDX (The Endocrine Disruption Exchange), whose goal is to reduce the production, use, and exposure to chemicals that interfere with human development and function. TEDX's mission is to provide objective technical information to a wide range of clientele including policy makers. For my complete CV, see http://www.endocrinedisruption.com/files/Theo-CV-090115.pdf

I am here to speak to you about the implications of the widespread distribution of endocrine disrupting chemicals in the environment. In order to do this, it is particularly important to first understand what the endocrine system is and how endocrine disrupting chemicals work. I am sure that every one of you knows what



The Endocrine System

and where the sex organs are and know about the male hormones that include testosterone, and the female hormones that are estrogenic -- because they play a very important role in making sure we perpetuate our species, and they get the most attention in the media. However, there are numerous other glands and hormones that get little attention that play a critical role in keeping us alive. Like the sex hormones, they play critical roles in how the fetus and embryo develop from fertilization to birth and even later as the newborn matures. They not only control the construction of the baby's vital systems but also play a part in programming the brain and behavior. If any of these components of the endocrine system are disturbed during gestation, the offspring may be deprived of the ability to live up to its fullest potential, which could be especially hazardous for wild animals that, almost from the moment they are born, or shortly thereafter, are pretty much on their own. They have no family or government agencies to help them cope with their disorders.

The brain is the most important part of the endocrine system. It acts through a thermostat-like feedback mechanism that controls the concentrations of hormones in the body in the range of parts-per-billion and parts-per-trillion. Even the development of the brain is strictly regulated by hormones.[1] The thyroid gland, along with the sex

[1] Takahashi M, Negishi T, Imamura M, Sawano E, Kuroda Y, Yoshikawa Y, Tashiro T. 2009. Alterations in gene expression of glutamate receptors and exocytosis-related factors by a hydroxylated-polychlorinated biphenyl in the developing rat brain. Toxicology 257:17-24.

glands, plays an important role in reproduction. It also plays a critical role in brain development and intelligence. The adrenals are very much involved with the integrity of the immune system and our response to stress; the corticosteroids are among their hormones. The adrenals also produce testosterone at critical stages during development and throughout life, and they produce hormones that control blood pressure. The pancreas is the source of another hormone, insulin, which controls sugar metabolism and which if disturbed, can lead to diabetes and obesity, disorders that have reached pandemic levels in the US.

Only within the past two decades has modern technology made it possible to prove that hormones operate at parts-per-billion and parts-per-trillion. And because of the exquisite sensitivity of this new technology we now know that many endocrine disrupting chemicals can enter the body through the skin, the lungs, and the mouth, and fool those brain thermostats and the hormone receptor sites in tissues and glands, causing improper development, function, and behavior -- at concentrations that some still insist are so low they are of no importance.

Those of us sitting here this morning could drink a cocktail of endocrine disrupting chemicals at concentrations found in the environment and not experience any change in how we feel –and perhaps not even suffer any permanent harm. But, if the same cocktail were to be ingested by a pregnant woman, those chemicals could enter the womb and alter the programming of her baby's brain and how its vital organs, tissues, and systems develop, causing it to need constant care the rest of its life. The timing of exposure to endocrine disrupting chemicals determines their toxicity and it is well documented that the embryonic and fetal stages of development are the most vulnerable. The increasing costs to society of these lifelong health problems are already astronomical.[2]

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[2] American Diabetes Association (ADA). 2008. Economic Costs of Diabetes in the U.S. in 2007. Diabetes Care 31:1-20.

Birnbaum HG, Kessler RC, Lowe SW, Secnik K, Greenberg PE, Leong SA, Swensen AR. 2005. Costs of attention deficit-hyperactivity disorder (ADHD) in the US: excess costs of persons with ADHD and their family members in 2000. Curr Med Res Opin 21:195-206.

Davies K. 2006. Economic costs of childhood diseases and disabilities attributable to environmental contaminants in Washington State, USA . EcoHealth 3:86-94.

Foundation for People with Learning Disabilites. 2007. Economic consequences of autism in the UK:4 pp. Accessible at: http://www.learningdisabilities.org.uk/publications?EntryId5=28948

Juvenile Diabetes Research Foundation International (JDRF). 2007. The Cost of Diabetes Continues to Grow. So Must Our Efforts to Stop It.:6 pp. Accessible at: http://www.jdrf.org/files/General_Files/Advocacy/2007/Advoc_piece_T1.pdf

Landrigan PJ, Schechter CB, Lipton JM, Fahs MC, Schwartz J. 2002. Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. Environ Health Perspect 110:721-728.

Leibson CL, Long KH. 2003. Economic implications of attention-deficit hyperactivity disorder for healthcare systems. Pharmacoeconomics 21:1239-1262.

Pelham WE, Foster EM, Robb JA. 2007. The economic impact of attention-deficit/hyperactivity disorder in children and adolescents . J Pediatr Psychol 32:711-727.

Pinock S. 2007. The Trials of Keeping Track. Autoimmune diseases attack millions of people around the world, but no one is quite sure how many people suffer or what these diseases take out of the world economy. Accessible at: http://www.the-scientist.com/2007/05/01/s16/1/

History

Although the phenomenon of endocrine disruption was first described in 1988,[3] its history dates back to 1972 when Pierre Trudeau and Richard Nixon signed the Great Lakes Water Quality Agreement (GLWQA) between Canada and the United States to clean up the Great Lakes and give the Canada/US International Joint Commission (IJC) the responsibility to report back to the parties, the US Congress and the Canadian Parliament, on a biennial basis. The GLWQA was signed because of reports that Lake Erie was dead; the Cuyahoga River was catching on fire; garbage and debris were being dumped directly into the lakes; drifting rafts of ugly foam were piling up on the beaches; vast lake regions were plagued with algal blooms; there were flagrant point-source industrial discharges into all the lakes, as well as excessive agricultural run-off; and dire stories from both Canadian and US wildlife biologists about the disappearance of wildlife species in the lakes. All of these were visible impacts which made it easy to convince authorities to take action.

By 1987 the physical appearance of the lakes had improved -- the overt evidence of pollution was reduced. But chemists, wildlife biologists, and child psychologists were reporting that something more insidious was going on. The animals at the top of the Great Lakes food web were suffering increasing losses, and the results of a couple of Lake Michigan[4] and Lake Ontario[5] healthy mother/infant studies were beginning to raise concern about behavioral and intelligence problems in the infants and children of mothers who ate fish from the lakes. Disturbing reports of correlations between organochlorine chemical body burden and the intensity of the effects were being reported in wildlife and human offspring. And in that year, 98% of the Canadians polled in eastern Canada felt that pollution in the Great Lakes was affecting their health.

Consequently, in 1987 the IJC Science Advisory Board requested a report on the state of the environment of the Great Lakes ecosystem from western Lake Superior to the mouth of the St. Lawrence River. It was during the preparation of a report that

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Smith DH, Malone DC, Lawson KA, Okamoto LJ, Battista C, Saunders WB. 1997. A national estimate of the economic costs of asthma. Am J Respir Crit Care Med 156(3 Part 1)):787-793.

Synergies Economic Consulting. 2007. Economic Costs of Autism Spectrum Disorder:141 pp. Accessible at: http://www.aeiou.org.au/files/Cost%20of%20autism%20report_FINAL_120507.pdf

[3] Colborn T. 1988. Great Lakes Toxics Working Paper. Government of Canada, Department of the Environment. [Contract Number KE 144-7-6336; 103 pp.]

[4] Fein GG, Jacobson JL, Jacobson SW, Schwartz PM, Dowler JK. 1984. Prenatal exposure to polychlorinated biphenyls: effect on birth size and gestational age. J Pediatr 105:315-320.

Jacobson JL, Jacobson SW. 1988. New methodologies for assessing the effects of prenatal toxic exposure on cognitive functioning in humans. In: Evans MS, ed. Toxic Contaminants and Ecosystem Health: A Great Lake Focus. New York: John Wiley & Sons. pp 373-388.

[5] Daly HB. 1992. The evaluation of behavioral changes produced by consumption of environmentally contaminated fish. In: Isaacson RL, Jensen KF, eds. The Vulnerable Brain and Environmental Risks, Vol. 1: Malnutrition and Hazard Assessment. Baltimore: University of Maryland. pp 151-171.

Environment Canada (EC) was preparing for the IJC assessment that endocrine disruption was first described in March, 1988. In its report EC provided a list of the adverse health effects found in 16 troubled, top predator birds, fish, mammals, and reptiles in the Great Lakes. Populations of these species had either disappeared or were in serious decline. Although the adult animals looked fine, their offspring, if they produced any, were not reaching sexual maturity and were incapable of reproducing. The health effects (see figure) that were causing the populations to crash included:

1. obvious reproductive impairment or loss of fertility;
2. eggshell thinning, a disturbance of endocrine-controlled calcium metabolism;
3. metabolic changes that led to wasting and early death even before chicks hatched or fry could swim up;
4. obvious birth defects, such as crossed bills and clubbed feet;
5. abnormal thyroid and male and female sex glands in almost all animals examined
7. abnormal thyroid hormone production in almost all fish and birds studied;
8. behavioral changes in birds, such as lack of parenting, nest inattentiveness, males forming fraternities rather than establishing territories and attempting to mate, and female/female pairing;
9. immune suppression, evidenced by increased rates of internal and external parasitism; and
10. the phenomenon of transgenerational exposure, where the maternal animals were passing the persistent organochlorine chemicals in their bodies to their offspring before they were born, through their blood, or with fish and birds through the liver to their eggs before they were laid.

Figure 6.1
Population, Organism, and Tissue Effects Found in Great Lakes Animals

Species	Population Decline	Reproduct. Effects	Eggshell Thinning	"Wasting"	Gross Defects	Tumors	Target Organ	Immune Suppress.	Behavioral Changes	Generational Effects
Bald eagle	x	x	x	x						x
Beluga whale	x		n/a		x	x	x	x		
Black-crowned night heron	x	x		x	x					
Caspian tern	x	x		x	x		x		x	x
Chinook/coho salmon	n/a	x	n/a			x	x			
Common tern	x			x			x	x	x	
Double-crested cormorant	x	x	x	x	x		x		x	x
Forster's tern	x	x	x	x	x		x		x	x
Herring gull	x	x	x	x	x		x	x	x	x
Lake trout	x	x	n/a	x					x	x
Mink	x	x	n/a	x			x			
Osprey	x	x	x							
Otter	x		n/a							
Ring-billed gull	x		x	x			x			
Snapping turtle	x	x		x	x		x			x

x = Observed effects that have been reported in the literature. Cells not marked do not necessarily mean there is no effect; only that no citation was found.

n/a = Not applicable.

Source: The Conservation Foundation.

None of the above problems correlated with habitat destruction, lamprey eel parasitism, or over-fishing, but they did correlate with the concentrations of organochlorine chemicals in the maternal animals. At that time, chemists were able to detect persistent organochlorine chemicals and pesticides at parts-per-million concentrations.

In 1990 The Conservation Foundation, Washington, D.C. and The Institute for Research on Public Policy, Ottawa, Ontario released a book, Great Lakes, Great Legacy?[6] that called for urgent action by federal, state, provincial, and local governments in both Canada and the US. The main message was that the standard toxicological protocols used to test chemicals for their safety had allowed the widespread use and dispersal of chemicals in the environment that could undermine development and function and pose threats to future generations -- and that risk assessment -- and toxicology -- had failed to protect us.

Then in 1991, a group of 21 experts from 17 different disciplines met at the Racine, Wisconsin Wingspread Center to share their research relative to the title of the conference, which became the title of a book, Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection. The wildlife biologists spoke first about what they had discovered in birds, fish, and mammals around the Great Lakes. Upon projecting on a huge screen slides of the abnormal glandular tissues in contaminated wild animals, those in attendance working with laboratory animal and human tissue were astonished. The slides could have been their own of the damage they could induce with chemicals in laboratory animals and what they were finding in the organs of humans exposed to an estrogenic pharmaceutical, diethylstilbestrol. Before the work session ended, the term, "endocrine disruption" was coined. The group also decided that they would each contribute a chapter to a book and they especially wanted to release a consensus statement as soon as possible about what they had learned. The consensus statement was released in September 1991, two months after the meeting (see Attachment 1).

The technical book was published in 1992[7] with the Consensus Statement as the first chapter. In the statement, the experts said they were certain that "A large number of man-made chemicals that have been released into the environment have the potential to disrupt the endocrine systems of animals including humans." They also stated with confidence that "Unless the environmental load of synthetic hormone disruptors is abated and controlled, large scale dysfunction at the population level is possible." At that time, they could not have perceived that only 18 years later, the developed world would be facing a pandemic of endocrine-related disorders from ADHD, autism, diabetes, obesity, childhood cancers, testicular cancer in young men, infertility, a

[6] Colborn T, Davidson A, Green SN, Hodge RA, Jackson CI, Liroff RA. 1990. Great Lakes, Great Legacy? The Conservation Foundation, Washington, D.C. and the Institute for Research on Public Policy, Ottawa, Ontario. xliii + 301 pp.

[7] Colborn T, Clement C, eds. 1992. Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection. Princeton, NJ: Princeton Scientific Publishing Co., Inc. (Mehlman MA, ed. Advances in Modern Environmental Toxicology, Vol. 21). xxi+403 pp.

syndrome called the male dysgenesis syndrome that includes undescended testicles, hypospadias, low sperm count, loss of semen volume and sperm quality, and increased risk of testicular and prostate cancer. All of the above disorders have increased significantly since the 1970s and have been traced back to prenatal exposure to endocrine disrupting chemicals.[8]

In 1996, shortly after the release of Our Stolen Future,[9] a popular press book that pieced the wildlife, laboratory animal, and human endocrine story together, Congress told the US EPA to design screens and assays to detect endocrine disruptors in the environment. The EPA has failed miserably[10] and now in 2009, regulatory agencies have no adequate testing tools to move forward as the list of known endocrine disrupting chemicals continues to grow (see Attachment 2).

2009 Closing Statement: The Problem

By ignoring the signals we were getting from wild animals, whose generation times are shorter than humans, we now find ourselves in a position where we have become dependent on and continue to produce and use vast amounts of chemicals that can disrupt the endocrine system. These chemicals are now widely dispersed in all aquatic systems and are moving in ocean currents and on the air at a global scale. Fortunately, following the release of the 1991 technical book, independent researchers around the world, stepping outside the bounds of their own disciplines through collaborative research, have begun to develop new approaches to detect chemicals that can interfere with development, function, and reproduction. Since 1991, it has been encouraging to track the increase in peer-reviewed publications in endocrine system research and, fortunately in the last decade, to move beyond the sex organs to the endocrine components in the brain, the thyroid, pancreas, adrenals, etc. making the links with the emerging disorders of pandemic proportions that can no longer be denied.

Chemists with increasingly efficient instrumentation and improved sample preparation protocols are discovering biologically active compounds in water and tissue from the equator to the poles. They are reporting increasing numbers and concentrations of industrial chemicals that have been in use for over 50 years, many of which were not detected in the past because they were treated as proprietary by the manufacturers, and for which only minimal and often disturbing health data are

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[8] Charboneau JP, Koger SM. 2008. Plastics, pesticides and PBDEs: Endocrine disruption and developmental disabilities. J Dev Phys Disabil 20:115-128.
Cottrell EC, Ozanne SE. 2007. Developmental programming of energy balance and the metabolic syndrome. Proc Nutr Soc 66:198-206.
Newbold RR, Padilla-Banks E, Jefferson WN, Heindel JJ. 2008. Effects of endocrine disruptors on obesity. Int J Androl 31:201-207.
Sharpe RM, Skakkebaek NE. 2008. Testicular dysgenesis syndrome: mechanistic insights and potential new downstream effects. Fertil Steril 89(2 Suppl.):e33-e38.

[9] Colborn T, Dumanoski D, Myers JP. 1996. Our Stolen Future. New York: Dutton. xii+306 pp.

[10] Colborn T, Environmental Health News. 2009 Apr 27. EPA's new pesticide testing is outdated. Scientific American website, accessible at: www.scientificamerican.com/article.cfm?id=epas-new-pesticide-testing-outdated .

available. Because they were protected as confidential their use was not revealed until they were found in the environment. In addition, pharmaceuticals and ingredients in cosmetics, personal care products, and household cleaning compounds, and plastics and resins in packaging material, toys, sporting goods equipment, old computers, automobiles, and electronic equipment of all kinds are now found regularly in rivers, lakes, seas, and oceans. Fossil-fuel derived plastics are piling up in garbage dumps around the world and circling thousands of miles in the surface waters of a huge North Pacific gyre[11] as they slowly fragment, degrade, and leach into both freshwater and saltwater systems at concentrations that have endocrine disrupting effects. One would think that society should have learned by now from the mistakes we have made. Yet today, using the current methods of extracting natural gas, we are deliberately introducing millions of gallons of fluids under extremely high pressure into the ground across vast land expanses in the US. These fluids are laced with known toxic chemicals, endocrine disrupting chemicals, and proprietary chemicals as if they are perfectly safe with little or no oversight or regulation.

It is now clear that a single chemical can have an impact on multiple systems, via several exposure pathways and via a number of modes of action, and expressed in multiple ways over the period of a lifetime.[12] These findings, that traditional toxicology continues to miss, have dire implications for public and environmental health. Although environmental concentrations of some of the persistent organochlorine chemicals have declined slightly over the past 10 years, they are still present at levels that cause measurable health impairment.[13] Using elegant new

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[11] Ludwig JP, Summer CL, Auman HJ, Gauger V, Bromley D, Giesy JP, Rolland R, Colborn T. 1997. The roles of organochlorine contaminants and fisheries bycatch in recent population changes in black-footed and Laysan albatrosses in the North Pacific Ocean. In: Robinson G, Gales R, eds. Albatross Biology and Conservation. Chipping Norton: Surrey Beatty & Sons. Pp. 225-238.

Moore CJ, Moore SL, Weisberg SB, Lattin GL, Zellers AF. 2002. A comparison of neustonic plastic and zooplankton abundance in southern California's coastal waters. Mar Pollut Bull 44:1035-1038.

Moore CJ. 2008. Synthetic polymers in the marine environment: A rapidly increasing, long-term threat. Environ Res 108:131-139.

[12] TEDX. 2009 Feb 10. Critical Windows of Development. Accessible at: http://www.endocrinedisruption.com/prenatal.criticalwindows.overview.php.

Barrett JR. 2009. Endocrine disruption: developmental picture window. Environ Health Perspect 117:A101.

[13] Cohn BA, Wolff MS, Cirillo PM, Sholtz RI. 2007. DDT and breast cancer in young women: new data on the significance of age at exposure. Environ Health Perspect 115:1406-1414.

Karmaus W, Osuch JR, Eneli I, Mudd LM, Zhang J, Mikucki D, Haan P, Davis S. 2009. Maternal levels of dichlorodiphenyl-dichloroethylene (DDE) may increase weight and body mass index in adult female offspring. Occup Environ Med 66:143-149.

Marsee K, Woodruff TJ, Axelrad DA, Calafat AM, Swan SH. 2006. Estimated daily phthalate exposures in a population of mothers of male infants exhibiting reduced anogenital distance. Environ Health Perspect 114:805-809.

Ribas-Fito N, Torrent M, Carrizo D, Munoz-Ortiz L, Julvez J, Grimalt JO, Sunyer J. 2006. In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. Am J Epidemiol 164:955-962.

Stahlhut RW, van Wijngaarden E, Dye TD, Cook S, Swan SH. 2007. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. Environ Health Perspect 115:876-882.

sensitive testing protocols to detect endocrine disruption, researchers are finding that these health problems are occurring at concentrations well below what was considered safe in earlier studies[14] and at what governments still deem safe today. It is important to add here that these new sensitive test protocols are not being used by government agencies for regulatory purposes, although this 21st century research, published in peer reviewed journals, has been funded by the US government and other governments around the world.

We learned about transgenerational exposure from wildlife in the Great Lakes, at a time when chemical contamination in the lakes got beyond the tipping point and caused the extirpation of some animal populations and others to almost disappear. Expanding what we learned from the Great Lakes experience, it did not take scientists long to confirm that among humans, embryos, fetuses, infants, and children are the most sensitive to endocrine disruption -- emphasizing the importance of protecting the womb environment so as not to risk the integrity of every newborn. Perhaps we should once again take another lesson from the wild and look seriously at the results of a study where a Canadian lake was dosed with ethinyl estradiol, the active ingredient in birth control pills. After only two years the fathead minnow population in the lake collapsed. The concentration of the birth control medication in the lake was 5-6 ppt, similar to what is discharged from municipal sewage treatment plants[15].

There can be no argument anymore that we face a dilemma stemming from a regulatory system that does not have a standardized assay or screen to confirm that a chemical is an endocrine disruptor. It is time to accept the fact that endocrine disruptors have duped the laws designed to protect public health. Cost benefit analysis and risk assessments have left us with a seriously contaminated environment. Hundreds of peer reviewed publications by independent researchers with no conflicts of interest demonstrate that numerous ubiquitous chemicals in the environment can interfere with development via the endocrine system, but there appears to be no will or authority to remove those chemicals from the supply chain in order to protect humans and wildlife.

If one looks carefully at the source of the long list of known endocrine disrupting chemicals almost every one is derived from natural gas, the by-products of processing natural gas and crude oil, and the burning of coal. The pandemics of endocrine-driven

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Torres-Sánchez L, Rothenberg SJ, Schnaas L, Cebrián ME, Osorio E, del Carmen Hernández M, García-Hernández RM, Constanza del Rio-Garcia C, Wolff MS, López-Carrillo L. 2007. *In* u*tero p,p´*-DDE exposure and infant neurodevelopment: A perinatal cohort in Mexico. Environ Health Perspect 115:435-439.

[14] Colborn T. 2006. A case for revisiting the safety of pesticides: A closer look at neurodevelopment. Environ Health Perspect 114:10-17.

Colborn T, Carroll L. 2007. Pesticides, sexual development, reproduction, and fertility: current perspective and future direction. Hum Ecol Risk Assess 13:1078-1110.

[15] Kidd KA, Blanchfield PJ, Mills KH, Palace VP, Evans RE, Lazorchak JM, Flick RW. 2007. Collapse of a fish population after exposure to a synthetic estrogen. Proc Natl Acad Sci USA 104:8897-8901.

disorders in the industrialized world, like climate change, are just another spin-off of society's addiction to fossil fuels.

Thank you for your time.

Attachment 1

Consensus Statement

Bern HA, Blair P, Brasseur S, Colborn T, Cunha GR, Davis W, Dohler KD, Fox G, Fry M, Gray E, Green R, Hines M, Kubiak TJ, McLachlan J, Myers JP, Peterson RE, Reijnders P.J.H., Soto A, Van Der Kraak G, vom Saal F, Whitten P. 1992. Statement from the Work Session on Chemically-Induced Alterations in Sexual Development: The Wildlife/Human Connection. In: Colborn T, Clement C, eds. Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection. Princeton, NJ: Princeton Scientific Publishing Co., Inc. (Mehlman MA, ed. Advances in Modern Environmental Toxicology; 21). pp 1-8

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

- 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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ACKNOWLEDGEMENT

Funding was provided by the Charles Stewart Mott Foundation, W. Alton Jones Foundation Inc., The Keland Endowment Fund of The Johnson Foundation and World Wildlife Fund.

* Although the research described in this article has been supported by the USEPA, it does not necessarily reflect the views of the Agency and no official endorsement should be inferred. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Attachment 2

Colborn article

Colborn T, Environmental Health News. 2009 Apr 27. EPA's new pesticide testing is outdated. Scientific American website, accessible at: www.scientificamerican.com/article.cfm?id=epas-new-pesticide-testing-outdated .

SCIENTIFIC AMERICAN

Perspectives - April 27, 2009

EPA's New Pesticide Testing Is Outdated

In its search for endocrine-disrupting chemicals, the agency should turn to new scientists, says an advocate

By Theo Colborn and Environmental Health News

The U.S. Environmental Protection Agency is ready to start testing 67 pesticide ingredients for their possible endocrine disruption effects. But the testing program the agency plans to use is only a pitiful skeleton of what it needs to be. This battery of tests, first recommended in 1998, is outdated, insensitive, crude, and narrowly limited.

Each test and assay was designed under the surveillance of corporate lawyers who had bottom lines to protect and assorted toxicologists who were not trained in endocrinology and developmental biology. For over a decade, EPA has ignored the vast wealth of information on endocrine disruption from independent academic researchers funded by the United States and other governments in Europe and Asia. This 21st century research is based on different assumptions than the toxicological assumptions that drove the EPA test designs. And most important, because of the limited scope of its test battery, EPA is not in a position to address the pandemics of endocrine-related disorders that pose a threat to every child born today.

The big question, of course, is how could this have happened? Well, from the very beginning, institutional barriers, bureaucratic inertia, and corporate interference led to one disconnection after another.

Starting in 1996, when Congress passed the new Food Quality Protection Action with the Federal Food, Drug, and Cosmetic Act Amendments, it told EPA to develop a screening program using tests and other scientifically relevant information to determine whether substances have hormonal activity. In response, EPA set up the Endocrine Disruptor Screening Program, including a committee with members representing the industries to be regulated, toxicologists, and a few token representatives from non-profit organizations. The scientists who discovered endocrine disruption and the hundreds of others, most of whom were not toxicologists and had shifted their research focus to the connections between a mother and her embryo and fetus, were not invited to participate. Instead of listening to those who knew something about endocrine disruption, EPA tried to use traditional toxicology protocols, forgetting that these had failed miserably and allowed endocrine disruptors to get through the government's programs to protect public health. EPA ignored the growing knowledge about endocrine disruption and trade associations representing corporations with deep pockets denied it. Consequently, EPA struggled along under the false assumptions that 'the dose makes the poison' and that high dose testing is sufficient to detect any chemical that can interfere with endocrine control of development and function.

Since the early 1990s, independent scientists in academic laboratories around the world have published hundreds of articles demonstrating how a broad selection of chemicals can interfere with the normal development of a baby at extremely low levels of exposure – in fact, levels similar to those experienced every day by people worldwide. These studies were done with the knowledge that the embryo and fetus develop under the control of hormones at parts per billion and parts trillion, and that as the baby matures hormone concentrations are regulated by sensitive, thermostat-like, feedback control systems in the brain. These pioneering scientists discovered effects for some widely used chemicals at concentrations thousands of times less than government "safe" levels of exposure derived through traditional toxicological tests. But their publications announcing damage in other components of the endocrine system, such as the pancreas, adrenal glands, bone, and mammary tissue, got no farther than headlines in newspapers. They had no effect on policy. While this wealth of knowledge was piling up, EPA, held back by institutional inertia, continued to attempt to validate a handful of single-focus assays to detect only a very small component of endocrine disruption. There was no connection between the assumptions of the toxicologists and those of the endocrinologists, developmental biologists, and the multi-disciplinarians doing the research needed to detect endocrine disruptors. This same disconnection was being played out in Europe where governments also continued to use outdated toxicological dogma.

One of the chemicals on EPA's list, atrazine, is a herbicide reported in aquatic and drinking water systems across the USA. It will likely pass this battery of tests with flying colors even though it feminizes laboratory animals and frogs by turning on the enzyme that converts testosterone to estrogen. EPA is proposing an assay to detect chemicals that can block that enzyme, but it cannot detect chemicals that turn it on.

EPA's testing program is full of voids, addressing only a segment of the organs, tissues, and systems that make up the endocrine system. It will not detect chemicals that can alter development and function of the pancreas, and its hormone, insulin, which could lead to diabetes and obesity. It also will not detect chemicals that alter how the brain is constructed and programmed that can undermine intelligence and behavior. An insecticide--like chlorpyrifos, which alters how brains develop and leads to measurable changes in behavior and function later in life--will probably not be picked up by the proposed tests.

In light of the increasing pandemics and the new administration's willingness to seek and make 180 degree changes, the time is ripe to move forward and let the scientists who understand the complexity of the endocrine system step in. Give these scientists, who have proven that they can think outside the box and inside the womb, the opportunity and wherewithal to design a couple of comprehensive, multi-organ assays to detect the most sensitive alterations in embryonic and fetal development and function. These assays that will ultimately reduce the use of thousands of animals and make up for the time lost over the past decade. Thanks to the internet, a rich set of data about endocrine disruption research is available, and with teleconferencing, scientists no longer have to leave their labs and travel long distances to communicate in large group sessions. These scientists are on the verge of developing protocols that will look nothing like what was done in the past to address a serious global health problem.

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This article originally ran at Environmental Health News, a news source published by Environmental Health Sciences, a nonprofit media company.