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## **Environmental Exposure to Endocrine Disruptors: What Are the Human Health Risks?**

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# Environmental Exposure to Endocrine Disruptors: What Are the Human Health Risks?

## Summary

Exposure to certain environmental pollutants may disrupt the human endocrine system causing adverse effects on development, growth, reproduction, metabolism, or other hormone-dependent processes, according to some scientists. Although there is no conclusive evidence to support this hypothesis, evidence is mounting, and research interest is growing. Chemicals of potential concern include certain pesticides (e.g., DDT or lindane), medicinal drugs (e.g., synthetic hormones), naturally occurring plant hormones (e.g., in soy beans), and industrial compounds (e.g., polychlorinated biphenyls (PCBs)), some dioxins, lead, mercury, arsenic, and organotins. Potential sources of such chemicals include wastewater discharges, industrial releases, and consumer products. Research is being conducted to identify the range of potential health effects and vulnerable animal species (perhaps including humans), sensitive periods of development, and chemicals with endocrine-disrupting potential.

Proponents of the hypothesis that environmental exposure to endocrine disruptors may be affecting human health point to apparent increases in U.S. rates of certain cancers, reported declines in sperm counts in various nations, and some scientific evidence of increasing rates of some birth defects, thyroid disorders, attention deficit disorder, premature births, and premature puberty. There appears to be a worldwide increase in cases of testicular cancer, for which there is no clear cause. The reason for reported increases in rates of other cancers has not been determined: such increases may reflect improvements in diagnostic tools or reporting rather than increases in disease. Research on trends in male fertility has produced inconsistent results. In some nations, research found a decline in sperm quality over the last few decades and increasing rates of deformities of male reproductive organs until 1985 after which rates apparently stabilized. Any of these effects could be linked to hormone disruption, because they are hormone mediated, but such links have not been established. Although high doses of some chemicals have been shown to affect hormonal processes in people, sometimes beneficially and sometimes adversely, many scientists believe that environmental levels of potential disruptors are too low to influence human endocrine systems. The effect of long-term exposure to low levels of multiple endocrine disruptors is a key question for scientific research.

Research interest is spurred by evidence that the endocrine systems of some wildlife, especially fish, are being affected by environmental pollutants, the ubiquitous presence of some potential hormone disruptors in the environment at low levels, lack of scientific understanding of endocrine chemistry, and lack of exposure data.

Congress has mandated chemical screening to assess the potential of pesticides and drinking water contaminants to affect hormone systems. As evidence accumulates, legislators may decide to increase or decrease funding for the endocrine disruptor screening program, or to expand its requirements to include additional chemicals or hormone functions. This report provides references to additional sources of information. It will be updated as the issue warrants.

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# Environmental Exposure to Endocrine Disruptors: What Are the Human Health Risks?

## Background

**Endocrine Disruptors.** Endocrine disruptors<sup>1</sup> are chemical compounds in drugs, food, consumer products, or the ambient environment that can interfere with internal biological processes of animals that normally are regulated by their hormones. Development, growth, reproduction, and metabolism, for example, are hormone-dependent processes that might be affected by exposure to endocrine disruptors. Some endocrine disruptors exist naturally, for example, the phytoestrogens in some plants. Others are the products of human industry – e.g., some pesticides and pharmaceuticals.

Some endocrine disruptors are similar in form and action to natural hormones; these are called “hormone mimics.” The terms “environmental estrogen” and “xenoestrogen” are narrower, referring only to those chemicals that mimic the action of the female sex hormone estrogen. Other endocrine disruptors do not mimic, but otherwise modify the synthesis, secretion, transport, binding, action, or elimination of natural hormones. Some scientists prefer the more neutral but just as inclusive term “endocrine modulators” over the better known term “endocrine disruptors.”

Exposure to high levels of manufactured endocrine disruptors in the environment has been shown to harm insects, some vertebrate wildlife, and aquatic life by interfering with the action of reproductive and other hormones. Selected, peer-reviewed studies are described and references are cited below.<sup>2</sup> There also is scientific evidence that relatively low environmental levels of endocrine disruptors may be harmful, particularly when they bioaccumulate, exposing animals higher on the food chain to greater chemical concentrations. Some scientists hypothesize that

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<sup>1</sup>The endocrine system includes the glands (e.g., thyroid, pituitary gland, pancreas, ovaries, or testes) and their secretions (i.e., hormones), that are released directly into the body’s circulatory system (rather than through ducts). The endocrine system controls blood sugar levels, blood pressure, metabolic rates, growth, development, aging, and reproduction.

<sup>2</sup>The pesticide industry has studied and exploited chemicals that can disrupt the endocrine systems of insects. For example, synthetic juvenile hormone analogs control insect pests by interfering with the natural juvenile hormone, which suppresses metamorphic change during molting and induces production of egg yolk protein during ovarian development. The pesticides can act to enhance or obstruct these endocrine effects. Examples include phenoxypheoxy carbamate and methoprene. However, research on insecticides is not described below, because it appears to be less relevant than research on vertebrates to the question of human health effects from environmental exposures.

existing environmental levels of endocrine disruptors also may be harming human health.

**Congressional and Administrative Attention.** The U.S. Congress began investigating the effects of endocrine disruptors in the environment at a hearing in 1993.<sup>3</sup> Among those testifying at that hearing were several researchers who later published their findings in the book, *Our Stolen Future*.<sup>4</sup> It summarized studies by wildlife biologists, epidemiologists, and other scientists, and hypothesized that endocrine disruption by environmental pollutants might have caused observed increases in deformities and population declines of amphibians, evidence of declining human fertility, and alleged increases in human rates of breast, testicular, and prostate cancers, as well as endometriosis.

In the next few years, research produced evidence both for and against the hypothesis that environmental levels of endocrine disruptors are harming human and ecological health.<sup>5</sup> Congress continued to study the issue, and in 1996 concluded that there was a need to screen pesticides and drinking water contaminants for potential to disrupt endocrine systems. A screening program was established in the Food Quality Protection Act (Public Law 104-170) and the 1996 Amendments to the Safe Drinking Water Act (Public Law 104-182).

The Food Quality Protection Act (FQPA) Section 408(p)<sup>6</sup> directs EPA, not later than 3 years after August 3, 1996, to require validated tests to determine the potential of pesticides to produce effects in humans similar to those produced by naturally occurring estrogens or, at the discretion of the Administrator, other endocrine effects in humans. The mandate covers all registered pesticide ingredients (both active and inert), as well as other substances identified by the Administrator which might have

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<sup>3</sup>U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Health and the Environment. *Health Effects of Estrogenic Pesticides*. 103<sup>rd</sup> Cong., 1<sup>st</sup> Sess., Oct. 21, 1993. Washington, DC: U.S. Govt. Print. Off. (1994) 185 p.

<sup>4</sup>Colburn, Theo, Dianne Dumanoski, and John Peterson Myers. *Our Stolen Future: Are We Threatening Our Fertility, Intelligence, and Survival? A Scientific Detective Story*. New York: Penguin. (1996) 316 p.

<sup>5</sup>Initially, one of the most influential studies (“Synergistic activation of estrogen receptor with combinations of environmental chemicals.” Arnold, S.F., D.M. Klotz, B.M. Collins, et al. (1996) *Science*, v. 272, p. 1489-1492.) was later retracted, when the authors were unable to replicate their results (McLachlan, J.A. (1997) “Synergistic effect of environmental estrogens: report withdrawn.” *Science*, v. 277, p. 459-463.) The original report indicated that effects of combined exposure to two different pesticides could be greater than effects from an equivalent exposure to either of the individual pesticides alone. However, synergy (as well as antagonism, in which effects are less than expected from exposure to a combination of chemicals) has been demonstrated for other health effects of exposure to PCBs and several pesticide formulations (Hook, G.E., and G.W. Lucier. (1997) “Editorial: Synergy, antagonism, and scientific processes.” *Environmental Health Perspectives*, v. 105, p. 784.)

<sup>6</sup>See §405 of P.L. 104-170, amending §408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a).

a cumulative effect together with pesticides and to which a substantial population may be exposed.<sup>7</sup>

The 1996 Safe Drinking Water Act Amendments (P.L. 104-182) authorize screening for endocrine disruption potential of contaminants found in sources of drinking water.<sup>8</sup> Actual screening of chemicals for toxic effects will be conducted by manufacturers of suspect chemicals. For substances found to have endocrine effects in humans, the laws authorize EPA to take appropriate action to protect public health under existing statutory authority.<sup>9</sup>

To help implement the new provisions, EPA organized the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC). This committee of scientists (some independent and others representing various chemical manufacturers and distributors, chemical users, public health advocates, environmentalists, and other stakeholder groups), assisted EPA in designing the chemical screening and testing program. The committee's recommendations, released October 5, 1998, were reviewed by a special peer review panel consisting of members of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Science Advisory Panel and the independent Science Advisory Board. EPA relied heavily on EDSTAC recommendations in developing the Endocrine Disruptor Screening Program.<sup>10</sup> Although the program was designed and "established" in 1998, it is not yet operating. EPA is still developing the methods that will be used to prioritize chemicals for screening and is attempting to validate the methods that will be used to test high-priority chemicals. In addition, a new Endocrine Disruptor Method Validation Subcommittee has been established to advise EPA on how it should evaluate the screens and tests developed. The Subcommittee met for the first time in December 2001. The program is not yet operational.

**Current Research Initiatives.** The hypothesis that existing environmental levels of endocrine disruptors may be harming human health is hotly debated. At present, there is no conclusive evidence to support this hypothesis, but research interest is growing. Scientists are working to better define the range of potential health effects and to identify vulnerable animal species and chemicals with endocrine-disrupting potential. Attention has focused on certain chemicals that are ubiquitous at low levels in the air, surface water, and food, and at higher levels in many consumer products, including medical devices and baby toys. Chemicals of potential concern include a number of pesticides (e.g., DDT, lindane, and vinclozolin), medicinal drugs (especially synthetic hormones), and certain industrial

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<sup>7</sup>The EPA Office of Science Coordination and Policy website describes the statutory authority for the Endocrine Disruptor Screening Program.  
[<http://www.epa.gov/scipoly/oscpendo/>]

<sup>8</sup>See §136 of P.L. 104-182, adding a new §1457 to the Safe Drinking Water Act (42 U.S.C. 300j-17).

<sup>9</sup>Federal Food, Drug, and Cosmetic Act, as amended; 21 U.S.C. 346a(p)(6).

<sup>10</sup>U.S. Environmental Protection Agency. "Environmental Protection Agency Endocrine Disruptor Screening Program, Report to Congress." August 2000. p. 5.

compounds (e.g., phthalates, bisphenol A, polychlorinated biphenyls (PCBs), some dibenzodioxins, lead, methyl mercury, arsenic, and organotins).

Many U.S. and other governmental and intergovernmental organizations are sponsoring and coordinating research efforts to clarify the scope and severity of potential endocrine disruptor effects. In the United States, work within federal public health and environmental agencies is being coordinated by the Endocrine Disruptor Working Group, which was established by the National Science and Technology Council's Committee on the Environment and Natural Resources.<sup>11</sup> Internationally, the Organization for Economic Cooperation and Development (OECD) is developing harmonized international test guidelines to detect endocrine disruptors.

## Scientific Evidence

**Human Health Trends.** Proponents of the hypothesis that environmental exposure to endocrine disruptors may be affecting human health have pointed to apparent increases in U.S. rates of certain cancers, reported declines in sperm counts in various nations, and some scientific evidence of increasing rates of some birth defects, thyroid disorders, attention deficit disorder, premature births, and premature puberty. In fact, there appears to be a worldwide increase in the incidence of testicular cancer, for which there is no clear cause.<sup>12</sup> Reported rates of other human cancers also have increased, but these increases may reflect improvements in diagnostic tools or reporting rates rather than increased rates of disease.

Research in some nations has found a decline in semen quality<sup>13</sup> over the last few decades and increasing rates of deformities of male reproductive organs (i.e., undescended testes and misplaced urethra opening) before 1985, after which rates stabilized.<sup>14</sup> Some researchers also have reported increased rates of thyroid dysfunction, attention deficit disorder, and premature births, as well as a trend toward onset of puberty at an earlier age. Any of these effects could be linked to hormone disruption because they are hormone mediated, but such links have not been established.

**Human Evidence of Potential Chemical Toxicity to Endocrine Systems.** The hypothesized link between human health problems and the disruption of hormone activity as a result of exposure to chemicals in the environment is biologically plausible; some chemicals have been shown to affect

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<sup>11</sup>For more information about this group, see EPA's website on the Endocrine Disruptors Research Initiative.  
[<http://www.epa.gov/endocrine/>]

<sup>12</sup>Safe, S.H. (2000) Endocrine disruptors and human health: Is there a problem? An update. *Environmental Health Perspectives*, v. 108, n. 6, p. 487-493.

<sup>13</sup>Semen quality is based on ejaculate volume, sperm concentration, sperm motility, and sperm morphology.

<sup>14</sup>Safe, *ibid.*

hormonal processes in people and wildlife,<sup>15</sup> especially if the chemical is directly administered or otherwise received in a concentrated dose during fetal or infant development. For example, it is well known that daughters born to women who took the drug diethylstilbestrol (DES), a synthetic estrogen, early in their pregnancies between the mid 1940s and 1971, now have a greatly increased risk of vaginal cancer.<sup>16</sup> In addition, studies have documented a higher than normal incidence of genital tract abnormalities in newborns following *in utero* exposure to DES.<sup>17</sup> The role of male and female sex hormones in the growth of prostate and breast cancer is well established scientifically.<sup>18</sup>

Although the production and use of PCBs has been strictly regulated since 1976, PCBs are ubiquitous in the air, water, soil, and many animal tissues due to their environmental persistence and previously widespread use in electrical transformers, plastics, and other industrial applications. Some PCBs are known to be estrogenic; others may affect thyroid function.<sup>19</sup> There is evidence that fetal exposure to PCBs may affect cognitive development, although it is not known whether this toxicity is related to hormone disruption.<sup>20</sup> In addition, some studies have found an association

<sup>15</sup>Generally, scientists have studied effects in vertebrates, especially amphibians, freshwater fish, and mammals.

<sup>16</sup>Herbst, A., H. Ulfelder, and D. Poskanzer. "Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women," *New England Journal of Medicine*, v. 284, (1971) p. 878-881.

<sup>17</sup>Mittendorf, R. Teratogen update: Carcinogenesis and teratogenesis associated with exposure to diethylstilbestrol (DES) in utero. *Teratology*, v. 51, n. 6, (1995) p. 435-445.

<sup>18</sup>See the National Cancer Institute website at [<http://www.nci.nih.gov>]

<sup>19</sup>Longnecker, M.P., W.J. Rogan, and G. Lucier. The human health effects of DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated biphenyls) and an overview of organochlorines in public health. *Annual Review of Public Health*, v. 18, p. 211-244. (1997)

Brouwer, A., U.G. Ahlborg, F.X. van Leeuwen, and M.M. Feeley. Report of the WHO working group on the assessment of health risks for human infants from exposure to PCDDs, PCDFs and PCBs. *Chemosphere*, v. 37, n. 9-12, p. 1627-1643. (1998)

<sup>20</sup>Stewart, P., J. Reihman, E. Lonky, T. Darvill, and J. Pagano. (2000) Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. *Neurotoxicology and Teratology*, v.22, n. 1, p. 21-29.

Jacobson, J.L., S.W. Jacobson, and H.E. Humphrey. (1990) Effects of exposure to PCBs and related compounds on growth and activity in children. *Neurotoxicology and Teratology*, v. 12, n. 4, p. 319-26.

Patandin, S., C.I. Lanting, P.G. Mulder, E.R. Boersma, P.J. Sauer, and N. Weisglas-Kuperus. (1999) Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age [see comments]. *Journal of Pediatrics*, v. 134, n. 1, p.33-41.

Jacobson, J.L., and S.W. Jacobson. (1996) Intellectual impairment in children exposed to polychlorinated biphenyls *in utero* [see comments]. *New England Journal of Medicine*, v. 335, n. 11, p. 783-789.

Jacobson, J.L., and S.W. Jacobson. (1996) Dose-response in perinatal exposure to polychlorinated biphenyls (PCBs): the Michigan and North Carolina cohort studies.

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between human PCB exposure and low sperm counts, undescended testes, altered semen quality, lower age of onset of puberty, and shorter height at maturity.

Such developmental, reproductive, and carcinogenic effects for which increased incidences have been reported in humans are similar to effects on reproductive structure and function that have been observed in wildlife and fish exposed to endocrine disruptors.<sup>21</sup>

On the other hand, some chemicals with effects on endocrine systems have therapeutic value. For example, sex hormones are used to treat some forms of cancer. There also is evidence that some plant-derived endocrine disruptors<sup>22</sup> (e.g., phytoestrogens prevalent in soy beans) may protect against disease.<sup>23</sup> Some scientists argue that such evidence undermines the hypothesis that endocrine disruptors in the environment are a threat to human health. Other scientists believe the evidence for therapeutic effects only underscores the potency of hormonally active chemicals.

**Animal Evidence.** The most compelling evidence for endocrine disruption due to environmental exposure to contaminants has been obtained in aquatic systems, with most of the published literature based on studies of fish.<sup>24</sup> In particular, feminization of males due to endocrine disrupting chemicals is an increasing concern. Feminization has also been reported in other vertebrate species including birds (especially fish-eating species, such as gulls, terns, ospreys, eagles, and pelicans) and Florida panthers.<sup>25</sup> In addition, there is evidence of harmful effects of endocrine disrupting chemicals on alligators<sup>26</sup> and mink<sup>27</sup> as well as circumstantial evidence

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<sup>20</sup>(...continued)

*Toxicology and Industrial Health*, v. 12, n. 3-4, p. 435-445.

<sup>21</sup>U.S. Environmental Protection Agency (1997). Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis, EPA/630/R-96/012. p. 5.

<sup>22</sup>Perhaps in this case, the term endocrine modulator is more appropriate.

<sup>23</sup>Vincent, A. and L.A. Fitzpatrick. (2000) Soy isoflavones: are they useful in menopause? *Mayo Clinic Proceedings*, v. 75, n. 11, p. 1174-1184.

Stephens, F.O. (1997) Breast cancer: aetiological factors and associations (a possible protective role of phytoestrogens). *The Australian and New Zealand Journal of Surgery*, v. 67, n. 11, p. 755-760.

<sup>24</sup>Jobling, Susan, et al. (1998) "Widespread sexual disruption in wild fish," *Environmental Science and Technology*, v. 32, p. 2498-2506.

<sup>25</sup>Facemire, Charles F., Timothy S. Gross, and Louis J. Guillette, Jr., (1995) "Reproductive impairment in the Florida panther: nature or nurture?" *Environmental Health Perspectives*, v. 103, Supp. 4, p. 79-86.

<sup>26</sup>Guillette, Louis J., et al. (1995) "Gonadal steroidogenesis *in vitro* from juvenile alligators obtained from contaminated or control lakes," *Environmental Health Perspectives*, v. 103, no. 4, p. 31-36.

<sup>27</sup>Golub, Mari S., James M. Donald, and Joe A. Reyes. (1991) "Reproductive toxicity of commercial PCB mixtures: LOAELs and NOAELs from animal studies," *Environmental Health Perspectives*, v. 94, p. 245-253.

for marine mammals.<sup>28</sup> For example, the accumulation of persistent chlorinated organic chemicals, such as PCBs, in seals and dolphins has been well documented.<sup>29</sup> In addition, laboratory studies of a beluga whale protein that is key in many endocrine disrupting effects (the aryl hydrocarbon receptor) reveal that it binds strongly to dioxins and PCBs. This may increase the likelihood that toxic responses can be turned on at physiologically relevant concentrations of contaminants.<sup>30</sup> However, as is the case with humans, direct toxicity testing in marine mammals is precluded by logistical, legal, and ethical constraints, which make cause-and-effect relationships difficult (or impossible) to show experimentally.

Feminization of male fish collected from British rivers alerted the scientific community to the potential hazard of chemicals (in those cases, xenoestrogens) in the environment.<sup>31</sup> Feminization of males was confirmed by the presence of eggs in the testes and the female-specific yolk protein vitellogenin (a component of yolk for eggs, usually made only by females) in the blood of male fish. While manufacture of vitellogenin by males is clearly abnormal, it is not clear whether these males are impaired in their normal male reproductive function. More recently, marine fish populations in the English Channel and in Tokyo Bay have also shown evidence of feminization. Less information is available for the United States. However, there is a report of complete sex reversal of male salmon in Washington.<sup>32</sup> Androgenic substances (i.e., substances with an effect similar to that of male sex hormones) have also been detected in environmental samples, especially in pulp mill effluents.

Bony fish<sup>33</sup> appear to be useful as sentinels for the presence and possible hazard of endocrine disrupting chemicals in the aquatic environment, since these fish are currently the only vertebrates for which the connection between environmental

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<sup>28</sup>Cooper, Ralph L., and Robert J. Kavlock. (1997) "Commentary: endocrine disruptors and reproductive development: a weight-of-evidence overview," *Journal of Endocrinology*, v. 152, n. 2, p. 159-166.

Ross, Peter S. (2000) "Marine mammals as sentinels in ecological risk assessment," *Human and Ecological Risk Assessment*, v. 6, p. 29-46.

<sup>29</sup>Watanabe, M., K. Kannan, A. Takahashi, et al. (2000) "Polychlorinated biphenyls, organochlorine pesticides, tris(4-chlorophenyl)methane, and tris(4-chlorophenyl)methanol in livers of small cetaceans stranded along Florida coastal waters, USA," *Environmental Toxicology and Chemistry*, v. 19, n. 6, p. 1566-1574.

Reddy, M.L., J.S. Reif, A. Bachand, et al. (2001) "Opportunities for using Navy marine mammals to explore associations between organochlorine contaminants and unfavorable effects on reproduction," *Science of the Total Environment*, v. 274, n. 1-3, p. 171-182.

<sup>30</sup>Jensen, Brenda A., and Mark E. Hahn. (2001) "cDNA cloning and characterization of a high affinity aryl hydrocarbon receptor in a cetacean, the beluga, *Delphinapterus leucas*," *Toxicological Sciences*, v. 64, p. 41-56.

<sup>31</sup>Jobling, Susan, et al. (1998) "Widespread sexual disruption in wild fish," *Environmental Science and Technology*, v. 32, p. 2498-2506.

<sup>32</sup>James J. Nagler, James J., et al. (2001) "High incidence of a male-specific genetic marker in phenotypic female Chinook salmon from the Columbia River," *Environmental Health Perspectives*, v. 109, n. 1, p. 67-69.

<sup>33</sup>As opposed to cartilaginous fish, such as sharks and rays.

contamination and adverse effects on organism health has been established in both field<sup>34</sup> and laboratory<sup>35</sup> studies. The aquatic environment is especially well suited for these studies as it is the ultimate sink for many natural and anthropogenic compounds released into the environment. Fish, in turn, are well suited for such research as our understanding of their endocrinology is far superior to that of aquatic invertebrates. Both androgenic<sup>36</sup> and estrogenic<sup>37</sup> effects have been observed and published, with

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<sup>34</sup>Folmar, Leroy C., et al. (2001) "Vitellogenin-induced pathology in male summer flounder (*Paralichthys dentatus*)," *Aquatic Toxicology*, v. 51, p. 431-441.

Folmar, Leroy C., et al. (1996) "Vitellogenin introduction and reduced serum testosterone concentrations in feral male carp (*Cyprinus carpio*) captured near a major metropolitan sewage treatment plant," *Environmental Health Perspectives*, v. 104, p. 1096-1100.

Harries, J.E., et al. (1997) "Estrogenic activity in five United Kingdom rivers detected by measurement of vitellogenin in caged male trout," *Environmental Toxicology and Chemistry*, v. 16, p. 534-542.

Jobling, Susan, et al. (1998) "Widespread sexual disruption in wild fish," *Environmental Science and Technology*, v. 32, p. 2498-2506.

<sup>35</sup>Panter, Grace H., R. S. Thompson, and John P. Sumpter. (1998) "Adverse reproductive effects in male fathead minnows (*Pimephales promelas*) exposed to environmentally relevant concentrations of the natural oestrogens, oestradiol and oestrone," *Aquatic Toxicology*, v. 42, n. 4, p. 243-253.

<sup>36</sup>Galloway, Brendan, et al. (2000) "Examination of the cumulative responses of slimy sculpin (*Cottus cognatus*) and white sucker (*Catostomus commersoni*) collected on the Saint John River downstream of a pulp mill, paper mill, and sewage discharges," *Society of Environmental Toxicology and Chemistry (SETAC)*, p. 255, SETAC: Nashville, TN.

Joakim Larsson, D.G., et al. (1999) "More male embryos near a pulp mill," In *6th International Symposium on the Reproductive Physiology of Fish*, (ed. B. Norberg, et al.), Bergen, Norway.

Munkittrick, Kelly R. et al. (1999) "Secondary sex characteristics and gonadal size in white sucker (*Catostomus commersoni*) during modernization at a pulp mill," In *6th International Symposium on the Reproductive Physiology of Fish*, (ed. B. Norberg, et al.), Bergen, Norway.

<sup>37</sup>Bayley, Mark, Jacob R. Nielsen, and Erik Baatrup. (1999) "Guppy sexual behavior as an effect biomarker of estrogen mimics," *Ecotoxicology and Environmental Safety*, v. 43, p. 68-73.

Bjerselius, Rickard, et al. (1999) "Estrogen in food or water severely effect the male goldfish (*Carassius auratus*) sexual behavior," In *6th International Symposium on the Reproductive Physiology of Fish*, (ed. B. Norberg, et al.), Bergen, Norway.

Haek, R.A., et al. (1997) "During development, 17 $\alpha$ -estradiol is a potent estrogen and carcinogen," *Environmental Health Perspectives*, v. 105, p. 577-581.

Jobling, Susan, et al. (1996) "Inhibition of testicular growth in rainbow trout (*Oncorhynchus mykiss*) exposed to estrogenic alkylphenolic chemicals," *Environmental Toxicology and Chemistry*, v. 15, p. 194-202.

Kime, David E., and Jon P. Nash, (2000) "Estrogenic endocrine disruptors act on many components of reproduction, over multiple generations to cause reproductive failure in zebrafish (*Dania rerio*)," In *4th International Symposium on Fish Endocrinology*, p. Poster, Seattle, WA.

Kramer, V.J., et al. (1998) "Reproductive impairment and induction of alkaline-labile phosphate, a biomarker of estrogen exposure, in fathead minnows (*Pimephales promelas*) exposed to waterborne 17 $\beta$ -estradiol," *Aquatic Toxicology*, v. 40, p. 335-360.

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estrogenic activity appearing to be more ubiquitous and hence better studied. It has become almost routine in laboratories around the world to isolate xenoestrogens from the aquatic environment, expose fish to the isolated compounds in the laboratory, and achieve similar endocrine modulation (*i.e.*, vitellogenin induction) as was observed at the corresponding field site. Other endocrine modulating effects (e.g., hormone levels, behavior, reproductive success, intersex) are much less successfully reproduced in the laboratory. Currently laboratories in the United States, Europe, and Japan are working to develop a biomarker<sup>38</sup> to assess adverse health effects due to exposure to endocrine disrupting chemicals or xenoestrogens, in particular.

The endocrinology of most invertebrates is less well understood. Reproductive impairment has been noted in some species of snails exposed to very low amounts of tributyltin (TBT), a constituent in anti-fouling paints used on boats. This chemical causes female snails to grow male reproductive organs in addition to normal female ones, a condition called “imposex.” When this condition becomes severe, affected females cannot function as females or as males; the resulting reproductive failure caused severe population declines in some species. While the use of TBT in anti-fouling paints has been severely restricted in the United States (P.L. 100-333, Organotin Antifouling Paint Control Act of 1988) and European countries, it remains in use in other parts of the world. In addition, ambiguous genitalia have been found by the EPA in Maine bivalves, allegedly due to herbicides.<sup>39</sup>

In laboratory experiments with rodents, there is clear evidence that exposure to some endocrine disruptors affects the development of reproductive organs and causes tumor development. For example, one study found that exposure of newborn mice to genistein (a naturally occurring plant estrogen) at a level “within the range to which humans may be exposed in soy-based infant formulas” caused growths on oviducts that would impair fertility, and lack of certain cell masses indicating impaired ability to ovulate in every exposed mouse and in no mouse that was

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<sup>37</sup>(...continued)

Matthiessen, P. (1998) “Effects on fish of estrogenic substances in English rivers,” In *Principles and Processes for Evaluating Endocrine Disruption in Wildlife*, (ed. R. Kendall, *et al.*), p. 239-247, Pensacola, FL: SETAC Press.

Panter, Grace, R. S. Thompson, and John P. Sumpter. (1998) “Adverse reproductive effects in male fathead minnows (*Pimephales promelas*) exposed to environmentally relevant concentrations of the natural oestrogens, oestradiol and oestrone,” *Aquatic Toxicology*, v. 42, n. 4, p. 243-253.

<sup>38</sup>A biomarker is a biochemical, morphological, or functional change that indicates exposure, response, or potential susceptibility to an environmental substance or agent. Biomarkers are generally used to increase sensitivity, specificity, or response capacity, the objective being to establish a causal relationship between a chemical agent and its effect on an organism.

<sup>39</sup>Van Beneden, R.J., *et al.* (1993) “Implication for the presence of transforming genes in gonadal tumors in two bivalve mollusk species,” *Cancer Research*, v. 53, p. 2976-2979.

Van Beneden, R.J. (1996) “Comparative studies of molecular mechanisms of tumorigenesis in herbicide-exposed bivalves,” In *Interconnections between Human and Ecosystem Health* (eds. R. DiGiulio and E. Monosson), Chapman and Hall Ecotoxicology Series, London, England, p. 29-43.

unexposed, and uterine cancer in about one-third of the exposed mice and none of the unexposed mice.<sup>40</sup>

**Environmental Exposure to Potential Endocrine Disruptors.** Concern about possible human hormone disruption has been fueled by the limited information available about levels of potential hormone disruptors in the environment. It is known that some potential endocrine disruptors are heavily used and, in some cases, released to the environment. For example, wastewater effluent from sewage treatment plants contains many potential endocrine disruptors, including synthetic (pharmaceutical) hormones. Other potential endocrine disruptors are prevalent in certain foods, such as soy-based milk substitutes, because soy beans contain phytoestrogens (i.e., isoflavonoids) at relatively high levels.<sup>41</sup> Some argue that the high phytoestrogen concentrations in food far exceed concentrations of endocrine disruptors in the environment, implying that environmental exposures are likely to be relatively insignificant. However, this conclusion is not necessarily justified, because it is based on a comparison of apples with oranges, or rather a mixture of isoflavonoids and other phytohormones with a mixture of synthetic industrial compounds, including pharmaceuticals and other chemicals, each of which may exert a different biological effect and be more or less potent at various concentrations.

Of course, release of a chemical does not necessarily imply that environmental levels of exposure are toxic, even to vulnerable populations of animals or people. Available data are somewhat reassuring, because known potential disruptors of endocrine function generally are present in the environment at very low levels.<sup>42</sup> On the other hand, little is known about possible health effects for children of exposure to low levels of contamination, and there are no measurements at all of ambient concentrations for most chemicals in the environment, some of which may be affecting hormones. Many known hormone disruptors are ubiquitous at low levels, raising the question of long-term effects and possible additive or synergistic effects with continual exposure.<sup>43</sup> Foods and surface water often contain trace amounts of pesticides, and many consumer products contain low levels of endocrine modulators such as phthalates or bisphenol A. For example, PCBs and some dioxins are very persistent in the environment and are known to bioconcentrate in the food chain. Children are exposed to PCBs through breast milk, and by eating fish and other fatty

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<sup>40</sup>Newbold, R.R., E.P. Banks, B. Bullock, et al. (2001) "Uterine adenocarcinoma in mice treated neonatally with genistein," *Cancer Research*, v. 61, n. 11, p. 4325-4328.

<sup>41</sup>The isoflavonoids appear to exert both estrogenic and anti-estrogenic effects which are not completely understood.

<sup>42</sup>Toxicologists generally assume that toxicity increases with increasing levels of exposure. But concentrations of some chemicals measured in the environment are similar to those measured in the bodies of some healthy animals. Moreover, some scientists argue that low levels of exposure to hormones may exert a disproportionately large effect compared to higher doses.

<sup>43</sup>National Academy of Sciences (1999). *Hormonally Active Agents in the Environment*, National Academy Press, Washington, DC.

U.S. Environmental Protection Agency. (1997) Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis, EPA/630/R-96/012.

foods that contain relatively high concentrations of PCBs.<sup>44</sup> Children can also be exposed in the womb, as PCBs move across the placenta.

One reason for concern about potential human health effects from hormone disruptors is the high level of biological availability and potency of some pharmaceutical and agricultural chemicals that may be released to the environment. Synthetic hormones are an obvious example. Birth control compounds, synthetic estrogen for postmenopausal women, and synthetic thyroid hormone are three common contaminants of wastewater.

Potential toxicity (i.e., ability to adversely affect hormone function) and potential exposure are not necessarily sufficient to demonstrate significant public health or ecological risks. Knowledge about the range of potential health effects in immature, as well as mature wildlife and humans, and actual exposure measurements are needed to accurately assess risks. Existing data sometimes support conflicting views, leading to controversies about the extent to which people generally are exposed to endocrine modulators, whether very low levels of exposure potentially could affect human health, and whether exposure to very low levels of chemicals in the environment currently is affecting reproduction, fetal development, or other hormone-dependent functions in animal or human populations. Nevertheless, a panel convened by the National Academy of Sciences concluded –

Environmental [hormonally active agents] probably have contributed to declines in some wildlife populations, including fish and birds of the Great Lakes and juvenile alligators of Lake Apopka, and possibly to diseases and deformities in mink in the United States, river otters in Europe, and marine mammals in European waters. Such contaminants, along with inbreeding, might have contributed to the poor reproductive success of the endangered Florida panther and the increased embryonic mortality of the snapping turtle in the Great Lakes.<sup>45</sup>

Those skeptical of the disruptor hypothesis argue that mammals have homeostatic mechanisms to moderate small fluctuations in hormone levels, so they are unlikely to be overwhelmed by low levels of environmental exposure. To the argument that low concentrations of several chemicals may additively exert influence on those exposed, skeptics counter that multiple disruptors are just as likely to compete, resulting in combined effects that are less than additive.

Some on-going studies of developmental effects in rats have found effects on the reproductive organs from very low levels of exposure to DES and bisphenol-A, an ingredient in some plastic. Similarly, preliminary results indicate low-dose effects on the brain and immune system from genistein and nonylphenol (a chemical in detergents). An expert workshop to evaluate the data on low-dose effects of endocrine disruptors recently concluded that biological effects have been shown to occur following exposure to some estrogenic compounds at very low levels.<sup>46</sup> The

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<sup>44</sup>Longnecker et al., *ibid.*

<sup>45</sup>National Academy of Sciences, p. 7.

<sup>46</sup>National Toxicology Program's Report of the Endocrine Disruptors Low Dose Peer (continued...)

question remains whether those effects would adversely affect human health, however.<sup>47</sup>

## Policy Issues

**Pace of FQPA Implementation.** Environmental, consumer, and public health advocacy groups accuse EPA of “dragging its feet” in implementing many provisions of the Food Quality Protection Act (FQPA), including the mandate to establish an endocrine disruptor screening program. The Natural Resources Defense Council (NRDC) and six California-based public interest groups alleged in a lawsuit filed August 3, 1999, in the U.S. District Court for the Northern District of California that delays had caused EPA to miss FQPA deadlines (*Natural Resources Defense Council v. U.S. Environmental Protection Agency*, No. C993701CAL). On January 19, 2001, EPA and NRDC agreed to settle the lawsuit. The settlement agreement states that endocrine disruptor screening will begin no later than spring 2004 (*Natural Resources Defense Council v. EPA*, No. C993701CAL, Jan. 19, 2001).

Although grower groups and the pesticide industry have echoed complaints about delays in overall FQPA implementation, they also have complained that EPA is proceeding too fast, jeopardizing the scientific basis for decisions about the screening program. Currently, few test protocols have been developed and validated for screening chemicals for endocrine disruption. Since chemical producers will conduct the actual screening of chemicals, they want to ensure that screening requirements established by EPA will be cost-effective in identifying potentially hazardous pesticides rather than wasteful of company resources. Thus, they generally would prefer relatively quick and inexpensive screens to quickly rule out (or at least delay) the need to pursue testing of chemicals that are less likely to pose health risks. This approach would allow time for additional, and perhaps improved, test methods to be validated. Public health advocates would prefer more thorough testing of a larger number of chemicals, to ensure that all potentially hazardous substances are identified and quickly regulated.

Some scientists are concerned about adopting and implementing a program at this time to screen chemicals for endocrine effects, because the field of study is so new and developing rapidly. Almost certainly, better tests will be developed as scientists gain understanding of the endocrine systems, how they develop, how they respond to variations in hormone levels, and how they might be disrupted. A key question then is how flexible the adopted program should be: Will it be allowed to evolve quickly in response to new knowledge? On the other hand, most scientists appear optimistic about the value of screening chemicals with the methods that are

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<sup>46</sup>(...continued)

Review. (2001) National Toxicology Program, U.S. Department of Health and Human Services.

[<http://ntp-server.niehs.nih.gov/htdocs/liason/LowDoseWebPage.html>]

<sup>47</sup>That is, the effects observed are not known to be adverse. For example, at certain very low doses fetal exposure to bisphenol-A produces enlarged prostates in male rats, but it is not clear that an enlarged prostate is an adverse health impact.

being developed, as long as they are validated prior to being employed on hundreds, if not thousands, of chemicals.

**Welfare of Test Animals.** Traditional methods of toxicity testing often involve administration of measured doses of chemicals to groups of laboratory animals (usually rodents), which are then observed for health effects. Test animals may be affected in a positive way (if the chemical at the administered dose improves health), unaffected, mildly adversely affected, severely adversely affected or even killed by the administered dose. If they survive (which generally is the scientifically preferable result), they may be sacrificed (i.e., killed) at some future date to permit internal inspection of tissues, or they may be allowed to live a normal lifespan. In some cases, test animals are allowed to reproduce, so that any adverse health effects on the reproductive process or on offspring may be observed. Standard scientific protocols generally require the use of groups of animals for such tests, so as to permit statistical analysis of the results. For example, many tests require the use of 25 or 50 rats of each gender at each dose level.

As mentioned above, few test protocols have been developed and validated for screening chemicals for endocrine disruption. At the end of August 2001, only one (the uterotrophic assay for estrogenic effects) of the 13 tests proposed for the endocrine disruptor screening program was validated, although work was proceeding on most of the other tests as well. According to the NRDC-EPA settlement agreement, all eight “tier 1” screening tests must be validated by December 2003, so that testing can begin in spring 2004. The second tier of five tests must be validated by December 2005.

Animal welfare advocates are concerned that a large number of animals might be sacrificed for the Endocrine Disruptor Screening Program, and they have questioned the value of such tests for assessing human health risks. They argue that alternatives to animal tests exist, and that others should be developed, both to improve the predictive value of the tests for human health and to protect the animals that otherwise might suffer or die.

For several years, federal agencies have been evaluating alternative methods for screening chemicals for toxicity, which would require the use of fewer laboratory rodents or other animals than are required using traditional toxicity tests. Alternative toxicity testing methods exist, but their results are more difficult to interpret, in terms of what they might mean for human health, and few are used routinely by federal agencies. The 103<sup>rd</sup> Congress established the Applied Toxicological Research and Testing Program within the National Institute of Environmental Health Sciences (NIEHS), in part, “to develop and validate assays and protocols, including alternative methods that can reduce or eliminate the use of animals in acute or chronic safety testing,” “to establish criteria for the validation and regulatory acceptance of alternative testing[,] and to recommend a process through which scientifically validated alternative methods can be accepted for regulatory use” (Public Law 103-43, Section 1301(a)). To implement the program, NIEHS established an ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The 106<sup>th</sup> Congress made ICCVAM a permanent interagency coordinating committee (Public Law 106-545). EPA is a member of this committee.



To date, ICCVAM has endorsed one alternative method, the so-called Up-and-Down Procedure, which reduces the number of rodents needed to evaluate acute toxicity.

Agencies reportedly are spending approximately \$13 to \$15 million to support research and development of endocrine disruptor methods in FY2002 and FY2003.<sup>48</sup>

## Legislation in the 107<sup>th</sup> Congress

The 107<sup>th</sup> Congress may consider proposals to increase or decrease funding for the endocrine disruption screening program, or to expand its requirements to include additional chemicals or endocrine effects. For example, S. 1712 in the 106<sup>th</sup> Congress would have required screening of substances discharged into the nation's water. Congress appropriated \$20.6 million for EPA's endocrine disruptor screening program and research in FY2000; \$22.9 million in FY2001; and \$20.3 million, the full amount requested in the President's budget, in FY2002. The House Committee on Appropriations urged EPA "to develop validation processes that incorporate the advice of the EDMVS" (Endocrine Disruptor Methods Validation Subcommittee), "and to provide a report to the Committee on the status of the EDMVS by March 15, 2002" (H. Rept. 107-159, p. 59).

Other legislative proposals in the 107<sup>th</sup> Congress (H.R. 1990, S. 855, and S. 940) would expand the reporting or regulatory requirements of other environmental statutes to cover chemicals with possible estrogenic or other hormonal effects. Such proposals may garner greater support if scientific evidence accumulates indicating significant adverse environmental or human health effects. On the other hand, ongoing studies may not substantiate claims of widespread adverse health or ecological effects of exposure to endocrine disruptors at environmental levels, leading to less support from appropriators and fewer proposals for additional research or regulation.

## Additional Resources

Additional information about endocrine disruptor science, the human health effect hypothesis, and the views of various stakeholders may be found on the World Wide Web. The views of the authors of *Our Stolen Future* and other environmental protection advocates may be explored at [<http://www.pmac.net/theos.htm>]. A skeptical view of the hypothesis that pollutants are disrupting the endocrine systems of humans and wildlife may be found at [<http://www.acsh.org/press/releases/endmod062999.html>]. EPA programs, policies and activities are summarized at [<http://www.epa.gov/scipoly/oscpendo/>]. A site that provides links to many other websites with information about endocrine disruptors is the Endocrine/Estrogen Letter at [<http://www.eeletter.com/links.htm>].

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<sup>48</sup>"Research on Endocrine Disruptor Exposure Focus of Grants from EPA, Other Agencies," *Daily Environment Report*, Nov. 1, 2001, p. A-7-8.