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

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Summary

In 2008, Congress banned the use in children's toys and child care articles of several chemicals known to disrupt normal development and reproduction of mice and rats. The legislation was a response to accumulating scientific evidence supporting the hypothesis that exposure to certain chemicals in consumer products and the environment might be adversely affecting human reproduction, growth, development, or metabolism by interfering with endocrine systems. This report, which supersedes CRS Report RL31267, summarizes the science underlying the environmental endocrine-disruptor hypothesis, and describes congressional actions and related programs and policy issues at the EPA.

This report focuses on the potential human health effects of environmental exposure to endocrine disruptors. The potential effects on fish and wildlife also are of concern. Scientists have discovered many egg-bearing male (intersex) bass in the Potomac River, as well as intersex fish of other species in other U.S. waters. Chemicals of interest include certain pesticides (e.g., DDT), synthetic hormones administered to cattle and poultry, both prescription and over-the-counter drugs and ingredients of some personal-care products (e.g.,triclocarban in antibacterial soaps), naturally occurring plant hormones (e.g., in soy beans), industrial compounds (e.g., polychlorinated biphenyls (PCBs)), some dioxins, lead, mercury, cadmium, uranium, arsenic, and organic compounds of tin. Potential sources of such chemicals include runoff from animal feedlots and agricultural fields, wastewater discharges, industrial releases, and consumer products.

Support might be found for the hypothesis that chemicals in the environment are disrupting human endocrine systems in the apparent increases in rates of certain cancers, reported declines in sperm counts, and reported 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. Any of these effects could be linked to hormone disruption, because they are hormone dependent and have been chemically induced in experimental animals. However, scientifically demonstrating a cause-effect relationship between environmental exposure to a particular chemical and human health effects is difficult. Many scientists hypothesize that environmental levels of potential endocrine disruptors are too low to influence human endocrine systems. Other scientists argue that significant adverse effects might result from long-term exposure to low levels of multiple endocrine disruptors.

Congress began investigating the presence and possible effects of endocrine disruptors in the environment at a hearing in 1993. In 1996, Congress directed the U.S. Environmental Protection Agency (EPA) to establish and implement an endocrine-disruptor screening program for pesticides and drinking water contaminants. As of January 2009, that program is still in development, funding for the program has declined, and legislators have expressed concern about the pace of program development. Some argue that it should not be launched until the complete test battery is validated. Others are concerned about the extent to which EPA might rely on animal experimentation in its screening program. Once the program is implemented, Congress might consider whether statutes and regulations provide adequate authority and direction with respect to the influence of any findings of endocrine disruption on the regulation of specific chemicals, chemical groups, uses, or products.

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Background

Scientific reports of reproductive failure among migratory birds exposed to DDT during the 1950s provided some of the earliest evidence that chemical pollutants in the environment might affect hormone-mediated processes in wildlife.[1] In 1996, several scientists brought the endocrine disruptor hypothesis to public attention with the release of a book, *Our Stolen Future*.[2] In the same year, Congress directed the U.S. Environmental Protection Agency (EPA) to develop and implement a program to screen all pesticides and suspect drinking water contaminants for endocrine disrupting potential. Ten years later, the screening program was not yet launched, when scientists reported finding a large number of feminized male fish in the Potomac River and other U.S. waters. In response, Congress held hearings and urged federal agencies to expedite related research. In 2008, the National Toxicology Program issued a report indicating scientific concern about fetal and child exposure to several chemicals with endocrine-disrupting potential. In the same year, Congress enacted legislation banning those chemicals in children's toys and child care articles.[3] Other legislation to regulate potential endocrine disruptors was pending at the end of the 110th Congress and may be re-introduced in the 111th Congress.

This report summarizes the science underlying the endocrine disruptor hypothesis, describes relevant congressional actions, outlines EPA's efforts to implement legislation, and discusses some policy issues that have been raised. The report is intended to support Congress as it considers legislation to control potential endocrine disruptors and as it oversees EPA's programs. With a few exceptions, the report does not discuss in detail all of the various specific chemicals that might be endocrine disruptors and particular source categories for such chemicals that might be in the environment. Several CRS reports on specific chemicals and sources are referenced where relevant.

Endocrine Disruptors

Endocrine disruptors[4] are chemical compounds in drugs, food, consumer products, or the ambient environment that can interfere with biological processes normally regulated by hormones within animals. Physical 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 (or plant estrogens, which are responsible for female sexual characteristics) in some plants. Others are the products of human industry – e.g., some pesticides and pharmaceuticals.

[1] Hoffman, David J., Barnett A. Rattner, G Allen Burton, Jr., and John Cairns, Jr. (Eds.) 2003. Handbook of Ecotoxicology. 2nd ed. Lewis Publishers: New York. p. 76.

[2] Colburn, Theo, Dianne Dumanoski, and John Peterson Myers. 1996. Our Stolen Future: Are We Threatening Our Fertility, Intelligence, and Survival? A Scientific Detective Story. New York: Penguin. 316 p.

[3] The chemicals banned were di-(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), or benzyl butyl phthalate (BBP). The ban was enacted through Section 108 of P.L. 110-314, the Consumer Product Safety Improvement Act of 2008.

[4] 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 metabolic rates, blood pressure, growth, development, aging, blood sugar levels, and reproduction.

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 hormones. (Similarly, environmental androgens are chemicals that mimic the action of the male sex hormones.) Other endocrine disruptors do not mimic, but block the action of hormones (for example, the anti-estrogens or anti-androgens) or 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 certain manufactured chemicals in the environment has been shown to harm insects, some vertebrate wildlife,[5] and aquatic life by influencing the normal activities or effects of reproductive and other hormones.[6] There also is scientific evidence that relatively low environmental levels of some chemicals may be harmful to the endocrine systems of fish and wildlife, particularly when low chemical concentrations are continuous or bioaccumulate, exposing animals higher on the food chain to greater chemical concentrations. Selected, peer-reviewed studies are described and references are cited under the next major section of this report, "Scientific Evidence." Some scientists hypothesize that existing environmental levels of potential endocrine disruptors also may be harming human health, but other scientists believe that current levels of such chemicals in the environment are too low to exert significant adverse effects on people.

Congressional and Administrative Attention

Congress began investigating the effects of endocrine disruptors in the environment at a hearing in 1993.[7] Among those testifying at that hearing were several researchers who later published their findings in the book, *Our Stolen Future*.[8] It summarized a number of studies by wildlife biologists, epidemiologists, and other scientists, and hypothesized that endocrine disruption by environmental pollutants might be responsible for increases in deformities and population declines of amphibians, declining human fertility in various geographical regions, and reported 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 that hypothesis.[9]

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[5] Generally, scientists have studied effects in vertebrates (animals with spines), especially amphibians, freshwater fish, and mammals.

[6] 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 phenoxyphenoxy carbamate and methoprene. However, research on insects 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. This is not meant to imply that any adverse effects on beneficial insects (such as the honeybee) might not be important. It is simply beyond the scope of this paper.

[7] U.S. Congress. House of Representatives, Committee on Energy and Commerce, Subcommittee on Health and the Environment. Health Effects of Estrogenic Pesticides. 103rd Cong., 1st Sess., Oct. 21, 1993. Washington, DC: U.S. Govt. Print. Off. (1994) 185 p.

[8] Colburn et al., 1996.

[9] Initially, one of the most influential studies ("Synergistic activation of estrogen receptor with combinations of environmental chemicals," S.F. Arnold, D.M. Klotz, and 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 (continued...)

Congress continued to study the issue, and in 1996 concluded that there was a need to screen pesticide chemicals and drinking water contaminants for their potential to disrupt endocrine systems. A screening program was established by the Food Quality Protection Act (P.L. 104-170) and the 1996 Amendments to the Safe Drinking Water Act (P.L. 104-182).

The Endocrine Disruptor Screening Program

The Food Quality Protection Act (FQPA) Section 408(p)[10] directs EPA, not later than three 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, as well as other substances identified by the Administrator which might have a cumulative effect together with pesticides and to which a substantial population may be exposed.[11]

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.[12] Under both statutes, actual screening of chemicals for toxic effects is to be conducted by manufacturers of suspect chemicals (or laboratories hired by manufacturers) following protocols approved by EPA. The laws authorize EPA to take appropriate action to protect public health under existing statutory authority if substances are found to have endocrine effects in humans.[13]

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 Science Advisory Board. EPA generally accepted the EDSTAC recommendations and officially "established" the Endocrine Disruptor Screening Program (EDSP) in 1998. Under this program, pesticides and other chemicals would be screened using a battery of tests known as Tier 1 assays, which are relatively inexpensive short-term tests. Chemicals that tested positive for possible endocrine disruption in one or more Tier 1 assays would be subjected to one or more Tier 2 toxicity tests, to confirm or refute Tier 1 results, and if confirmed, to determine the dose of the chemical that caused the effects. Tests would screen for effects on estrogen, androgen (hormones

(...continued)

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.)

[10] See §405 of P.L. 104-170, amending §408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a).

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

[12] See §136 of P.L. 104-182, adding a new §1457 to the Safe Drinking Water Act (42 U.S.C. 300j-17).

[13] Federal Food, Drug, and Cosmetic Act, as amended; 21 U.S.C. 346a(p)(6).

responsible for male sexual characteristics), and/or thyroid systems. The thyroid hormones regulate growth and development and the rate of metabolism.

Chemical screening for potential effects on endocrine systems has not yet begun, however, because EPA has not finished selecting and validating toxicity assays, the initial list of chemicals, and procedures for issuing EDSP orders to manufacturers.[14] An Endocrine Disruptor Method Validation Subcommittee (EDMVS) was formed in 2001 to advise EPA on how it should select and evaluate the screens and tests to be developed. This process proved to be controversial, particularly with respect to the role of animal experimentation and the validation of tests involving live animals. Three years later, the Endocrine Disruptor Methods Validation Advisory Committee (EDMVAC) was formed to replace EDMVS. This group has assisted EPA as it identified, developed, and validated the various methods for detecting potential endocrine disruptors.

In 2004 and 2005, the EDSP was reviewed and evaluated at EPA's request by the independent Board of Scientific Counselors (BOSC) for EPA's Office of Research and Development. A subcommittee of the BOSC prepared a final report, which is summarized in a peer-reviewed publication[15] and posted on the BOSC website.[16] The BOSC subcommittee concluded that the goals and science questions of the endocrine disruptor screening program were appropriate, and EPA's progress on implementing the program was good, although challenges remained. The subcommittee advised EPA to –

- strengthen its expertise in wildlife toxicology;
- expedite validation of the tests;
- take a leadership role in applying "omics" technologies (such as proteomics or metabolomics);
- maintain funding; and
- "continue to sponsor multidisciplinary intramural research and interagency collaborations."[17]

The BOSC again reviewed the program in 2008.[18] BOSC reported that the program

> ... exceeds expectations in progress to address concerns of the previous 2004 program review. ... The [Endocrine Disrupting Chemicals Research Program] has taken under consideration all recommendations of the previous BOSC review and those

[14] Draft lists and policies may be accessed through a consolidated EPA website at [http://www.epa.gov/scipoly/oscpendo/pubs/regaspects/index.htm].

[15] Harding, Anna K., George P. Daston, and Glen R. Boyd, et al. 2006. Endocrine disrupting chemicals research program of the U.S. Environmental Protection Agency: Summary of a peer-review report. Environmental Health Perspectives, v. 114, n. 8, p. 1276-1282.

[16] Board of Scientific Counselors, Office of Research and Development, U.S. EPA. Endocrine Disrupting Chemicals (EDC) Research Program Review, Final Report of the Subcommittee on Endocrine Disrupting Chemicals. March 4, 2005. Revised April 21, 2005, [http://www.epa.gov/OSP/bosc/pdf/edc0504rpt.pdf].

[17] Harding, ibid.

[18] Board of Scientific Counselors, Office of Research and Development, U.S. EPA. Mid-cycle Review of the Office of Research and Development's Endocrine Disrupting Chemicals (EDCs) Research Program at the U.S. Environmental Protection Agency, Apr. 16, 2008, [http://www.epa.gov/OSP/bosc/pdf/edcmc0804rpt.pdf].

> recommendations not implemented were held in abeyance because of budgetary constraints.[19]

The BOSC noted that –

> ... the budget to support this program has been cut substantially. The budget has been cut 20 percent since 2003, with a 4 percent cut proposed for this year. Funds for extramural STAR grants for EDC research were completely eliminated in 2005.[20]

Largely as a result of the constrained budget, BOSC found that wildlife toxicology and epidemiology remain areas of weakness in EPA's EDSP.[21]

EPA also has worked closely with the Interagency Coordinating Committee on the Validation of Alternative Methods (to identify and validate test methods that reduce animal use or suffering) and the Organization for Economic Cooperation and Development (to ensure international acceptance of the methods.)[22] EPA's independent Science Advisory Panel (established under the Federal Insecticide, Fungicide, and Rodenticide Act) has completed peer review of validated Tier 1 assays and approved EPA's initial test battery, but some chemical manufacturers continue to object to several of the Tier 1 assays. In July 2008, the Center for Regulatory Effectiveness (a public policy advocacy group) filed a "Request for Correction" on one of the assay validations under the Agency's Information Quality Guidelines (IQG), and Crop Life America, a trade group for pesticide manufacturers, filed a petition to delay the EDSP orders to initiate testing. As a result, EPA delayed the issuance of orders until 2009. An EPA website provides information about the status of program development, as of September 2008.[23]

At the same time that it was developing toxicity assays, EPA established a process for prioritizing and selecting chemicals to be screened.[24] In June 2007, EPA proposed a draft list of 73 chemicals for initial screening.[25] The comment period for the draft list ended February 11, 2008. The list included pesticide active ingredients, "selected based on their relatively high potential for human exposure"[26] and other chemicals produced in amounts greater than one million pounds per year that also are used in pesticide products but which are categorized as inert (that is, not active) pesticide ingredients. After considering comments on this list of chemicals, EPA is to issue a second *Federal Register* notice containing the final list of chemicals. EPA's website "EDSP Phases" provides additional details about the process EPA used to select chemicals for screening.[27] Early in 2008, EPA also solicited public comments about its proposed procedure for

[19] Ibid., Cover letter.

[20] Ibid., p. 5.

[21] Ibid., p. 6, 8.

[22] U.S. Congress. House of Representatives. Committee on Government Reform. Ova-Pollution in the Potomac: Egg-Bearing Male Bass and Implications for Human and Ecological Health. 109th Cong., 2nd Sess., Oct. 4, 2006. Washington, DC: Govt. Printing Off. (2006) p. 25 (Testimony of Benjamin H. Grumbles).

[23] EPA. EDSP Program Status Questions and Answers, [http://www.epa.gov/scipoly/oscpendo/pubs/regaspects/082808_qas.htm#augustquestions].

[24] Federal Register 56449, Sept. 27, 2005.

[25] Federal Register 33486, June 18, 2007.

[26] Federal Register 56449, Sept. 27, 2005.

[27] EPA. EDSP Phases, [http://www.epa.gov/endo/pubs/edspoverview/components.htm#4].

issuing orders to manufacturers to conduct toxicity testing and for overseeing compliance with such orders.[28]

The House Committee on Government Reform held a hearing October 4, 2006, to learn about the status of the EDSP and to examine the human and ecological health implications of the discovery of egg-bearing male bass in the Potomac River. One year later, some Members of that committee sent a letter to EPA Administrator Stephen L. Johnson asking him how EPA might speed up the process of screening chemicals for endocrine effects, to provide a timetable for EDSP implementation, and for explanations in response to specific questions about the process and substance of the program as designed.[29] EPA's responses are posted on the Committee's website.[30] The agency indicated that the list of chemicals, procedures, and peer review of Tier 1 tests should have been completed and Tier 1 test orders should have been issued to manufacturers of the first 73 chemicals before mid-2008. However, EPA did not meet that target date. The status of the program as of September 2008 may be determined by consulting the EPA website at http://www.epa.gov/endo/pubs/regaspects/082808_qas.htm.

Research Initiatives

The hypothesis that existing environmental levels of chemical pollutants may be harming human health by disrupting endocrine functions has been, and continues to be, hotly debated. At present, there is no conclusive evidence to support this hypothesis.

Research interest is growing, and some epidemiological studies have found statistical associations between human exposure and health effects that are consistent with the results of experiments with animals, particularly with respect to potential effects on prenatal and infant development. Research attention has focused on chemicals such as certain phthalates 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.[31] Some other chemicals of potential concern include a number of pesticides (e.g., DDT, lindane, and vinclozolin), medicinal drugs (especially synthetic hormones), other synthetic compounds (e.g., nonylphenol, polychlorinated biphenyls (PCBs), perchlorate), and some metals (e.g., lead, mercury, arsenic, and organotins). In recent years, hundreds of studies have been conducted to determine possible health effects due to exposure to components of plastics such as bisphenol A (BPA) and phthalates.[32] EPA has posted an inventory of endocrine research that it sponsors.[33]

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

[28] Federal Register 70845, Dec. 13, 2007, [http://www.epa.gov/endo/pubs/draft_policies_frn.pdf].

[29] Letter from Henry A. Waxman et al. to Administrator Johnson, Sept. 20, 2007, [http://oversight.house.gov/documents/20070920162537.pdf].

[30] EPA. Responses to Questions from the House of Representatives, Committee on Oversight and Government Reform, Chairman Henry Waxman, September 20,2007, [http://oversight.house.gov/documents/20071204153145.pdf].

[31] For more information about phthalates, see CRS Report RL34572, *Phthalates in Plastics and Possible Human Health Effects*, by Linda-Jo Schierow and Margaret Mikyung Lee.

[32] For more information about BPA, see CRS Report RS22869, *Bisphenol A (BPA) in Plastics and Possible Human Health Effects*, by Linda-Jo Schierow and Sarah A. Lister.

[33] EPA. Office of Research and Development. National Center for Environmental Research. Endocrine Disruptors Research. Research Projects, [.http://es.epa.gov/ncer/science/endocrine/researchproj.html].

effects.[34] In the United States, work among federal public health and environmental agencies was initially 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.[35] However, this working group appears to have disbanded after 1999. 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. and global rates of certain cancers,[36] reported declines in sperm counts in various nations,[37] and scientific evidence of increasing rates of type II diabetes,[38] obesity (especially among children),[39] some birth defects,[40] and other disorders.[41] In some cases, these reported increases in rates of hormone-mediated diseases or conditions may reflect improvements in diagnostic tools or reporting rates rather than increased rates of disease. In other cases, disease rates may have increased in fact, but may be due to medication use, smoking, or some other reason. However, in at least a few cases, increasing

[34] EPA. Office of Research and Development. National Center for Environmental Research. Science Topics. Endocrine Disruptors Research. Related Links, [http://es.epa.gov/ncer/science/endocrine/relatedlinks.html].

[35] For more information about this group, see the EPA website for the Endocrine Disruptor Research Initiative. However, the workgroup does not appear to be active, [http://www.epa.gov/endocrine/edrifact.html].

[36] Hodgson, N.C., J. Button, and C.C. Solorzano, et al. 2004. Thyroid cancer: is the incidence still increasing? Annals of Surgical Oncology, v. 11, n. 12, p. 1093-1097.

Jemal, A., R. Siegel, and E. Ward, et al. 2008. Cancer statistics, 2008. CA: A Cancer Journal for Clinicians, v. 58, n. 2, p. 71-96.

Sedjo, Rebecca L., Tim Byers, and Ermilo Arrera, Jr., et al. 2007. A midpoint assessment of the American Cancer Society challenge goal to decrease cancer incidence by 25% between 1992 and 2015. CA: A Cancer Journal for Clinicians, v. 57, n. 6, p. 326-340.

[37] Rozati, R., P.P. Reddy, and P. Reddanna, et al. 2000. Xenoesterogens and male infertility: myth or reality? Asian Journal of Andrology, v. 2, n. 4, p. 263-269.

Aitken, R.J., N.E. Skakkebaek, and S.D. Roman. 2006. Male reproductive health and the environment. Medical Journal of Australia, v. 185, p. 414-415.

Travison, T.G., A.B. Araujo, and A.B. O'Donnell, et al. 2007. A population-level decline in serum testosterone levels in American men. Journal of Clinical Endocrinology and Metabolism, v. 92, n. 1, p. 196-202.

[38] Lang, Iain A., Tamara S. Galloway, and Alan Scarlett, et al. 2008. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. Journal of the American Medical Association, v. 300, n. 11, p. 1303-1355.

[39] Hugo, Eric R., Terry D. Brandebourg, and Jessica G. Woo, et al., in press, "Bisphenol A at Environmentally Relevant Doses Inhibits Adiponectin Release from Human Adipose Tissue Explants and Adipocytes," Environmental Health Perspectives, online Aug. 14, 2008, at [http://www.ehponline.org/members/2008/11537/11537.pdf].

[40] Centers for Disease Control and Prevention, Department of Health and Human Services. Hypospadias trends in two US surveillance systems. Press Release Nov. 3, 1997, [http://www.cdc.gov/media/pressrel/hypospad.htm].

[41] Carpenter, D.O., Y. Shen, and T. Nguyen, et al. 2001. Incidence of endocrine disease among residents of New York areas of concern. Environmental Health Perspectives, v. 109, Supp. 6, p. 845-851.

Davis, Devra Lee, Pamela Webster, and Hillary Stainthorpe, et al. 2007. Declines in sex ratio at birth and fetal deaths in Japan, and in U.S. whites but not african americans. Environmental Health Perspectives, v. 115, n. 6, p. 941-946.

exposure to chemicals in the environment seems to some a plausible hypothesis to explain an increase in disease rates. Many developmental, reproductive, and carcinogenic conditions for which increased incidences have been reported in humans are similar to effects that have been observed in wildlife and fish exposed to endocrine disruptors.[42]

Congress has indicated its interest in several recent health trends, including: reported declines in certain nations in semen quality[43] over the last few decades; increasing rates of deformities of male reproductive organs before 1985, after which rates stabilized;[44] and a worldwide increase in the incidence of testicular cancer, for which there is no clear cause.[45] Some researchers have noted the similarity of these health concerns with effects seen in rats and mice prenatally exposed to certain phthalates that act as anti-androgens.[46] One hypothesis is that human exposure to combinations of phthalates and perhaps other ubiquitous endocrine disruptors might be interfering with the development of baby boys, resulting in what is referred to as "testicular dysgenesis syndrome."[47]

Human Studies of Chemical Effects on Endocrine Systems

Except for strong poisons with clear, short-term effects on health, the effects of chemical exposures on humans are difficult to demonstrate scientifically. Ethically, scientists cannot manipulate levels of human exposure to a chemical if there is a chance that harm might result. The alternative, so-called "natural experiments" (which compare the health of people with accidental exposures to the health of people with no exposure), is rare because accidental exposures of sufficient magnitude are few, and potentially contributing conditions (such as exposure to other chemicals) are inadequately controlled. In particular, study of effects of low-level exposures to environmental chemicals is problematic, because the expected effects are subtle and potentially affected by numerous conditions. Often, virtually everyone has been exposed to the chemical being studied, and there are too few unexposed people to serve as a control group for comparison.

Scientific studies have demonstrated the potential of hormones and some other chemicals acting through hormone systems to harm human health, especially if the chemical exposure is highly concentrated and occurs during fetal or infant development. For example, the role of naturally occurring male and female sex hormones in the growth of prostate and breast cancer is well established scientifically.[48] Moreover, research has demonstrated that administration of the drug

[42] U.S. Environmental Protection Agency. 1997. Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis, EPA/630/R-96/012. p. 5.

[43] Semen quality is based on ejaculate volume, sperm concentration, sperm motility, and sperm morphology.

[44] 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.

[45] Safe, ibid.

[46] Fisher, Jane S., S. Macpherson, and N. Marchetti, et al. 2003. Human 'testicular dysgenesis syndrome': a possible model using in utero exposure of the rat to dibutyl phthalate. Human Reproduction, v. 18, n. 7, p. 1383-1394.

Toppari, Jorma , John Chr. Larsen, and Peter Christiansen, et al. 1996. Male Reproductive Health and Environmental Xenoestrogens. Environmental Health Perspectives, v. 104, n. S4, online at http://www.ehponline.org/members/1996/Suppl-4/toppari.html.

[47] For more information about phthalates, see CRS Report RL34572, *Phthalates in Plastics and Possible Human Health Effects*, by Linda-Jo Schierow and Margaret Mikyung Lee.

[48] See the National Cancer Institute website at [http://www.nci.nih.gov].

diethylstilbestrol (DES), a strong, synthetic estrogen, to women early in their pregnancies greatly increases risk that their daughters will develop vaginal cancer and reproductive abnormalities.[49] In addition, studies have documented a higher than normal incidence of genital tract abnormalities in male babies following *in utero* exposure to DES.[50]

Some chemicals with effects on endocrine systems have therapeutic value. For example, sex hormones are used to treat some forms of cancer.[51] There also is evidence that some plant-derived endocrine disruptors[52] (e.g., phytoestrogens prevalent in soy beans) may protect against disease.[53] 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.

Numerous epidemiologic studies[54] have found associations between environmental levels of potential endocrine disruptors and effects on human development or health.[55] For example, a study of newborns in Spain reported data that suggested that the combined effects of bioaccumulated estrogenic substances in the placenta played a role in the risk of male urogenital malformations.[56] However, causality has not been (and possibly cannot be) clearly demonstrated for any adverse health effect as a result of exposure to an endocrine disruptor at levels typically present in the environment.

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[49] Herbst, A., H. Ulfelder, and D. Poskanzer. 1971. Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women. New England Journal of Medicine, v. 284, p. 878-881.

[50] Mittendorf, R. 1995. Teratogen update: Carcinogenesis and teratogenesis associated with exposure to diethylstilbestrol (DES) in utero. Teratology, v. 51, n. 6, p. 435-445.

[51] Huggins, Charles B. 1967. Endocrine-induced regression of cancers. Science, v. 156, n. 778, p. 1050-1054.

Machtens, S., D. Schultheiss, and M. Kuczyk, et al. 2000. The history of endocrine therapy of benign and malignant diseases of the prostate. World Journal of Urology, v. 18, n. 3, p. 222-226.

[52] Perhaps in this case, the term endocrine modulator is more appropriate.

[53] Warri, A., N.M. Saarinen, and S. Makela, et al. 2008. The role of early life genistein exposures in modifying breast cancer risk. British Journal of Cancer. v. 98, n. 9, p. 1485-1493.

Vincent, A. and L.A. Fitzpatrick. 2000. Soy isoflavones: are they useful in menopause? Mayo Clinic Proceedings, v. 75, n. 11, p. 1174-1184.

Lakshman, M., L. Xu, and V. Ananthanarayanan, et al. 2008. Dietary genistein inhibits metastasis of human prostate cancer in mice. Cancer Research, v. 68, n. 6, p. 2024-2032.

[54] "Epidemiologic" studies examine groups of people to determine rates of occurrence of particular outcomes (health effects) relative to varying levels of chemical exposure. Such studies rely on statistical methods to evaluate the likelihood of hypotheses about relationships between exposures and outcomes (that is, dose-response relationships). "Associations" are regular patterns between frequencies of particular health outcomes and changes in exposure levels. Associations do not necessarily indicate a causal relationship, but there can be no causal relationship without an association.

[55] Ibarluzea, J.M., M.F. Fernandez, and L. Santa-Marina, et al. 2004. Breast cancer risk and the combined effect of environmental estrogens. Cancer Causes and Control, v. 15, n. 6, p. 591-600.

Mocarelli, Paolo, Pier Mario Gerthoux, and Donald G. Patterson Jr., et al. 2008. Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Environmental Health Perspectives, v. 116, n. 1, p. 70-77.

Sharpe, Richard M., and D. Stewart Irvine. 2004. How strong is the evidence of a link between environmental chemicals and adverse effects on human reproductive health? British Medical Journal, v. 328, , n. 7437, p. 447-451.

[56] Fernandez, Mariana F., Begona Olmos, and Alicia Granada, et al. 2007. Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: A nested case-control study. Environmental Health Perspectives, v. 115, Supplement 1 (December), p. 8-14.

Most studies focus on a single chemical or closely related group of chemicals. For example, many scientists believe that the same phthalates that are toxic to rats and mice would be able to cause similar malformations in humans, because the male hormones affected by phthalates are important to the normal development of the male reproductive tract in *all* species of mammals. A few human studies have been conducted.[57] Some scientists have found that relatively low levels of exposure to phthalates may be associated with health effects. A study published in 2005 provided the first evidence of subtle developmental effects in baby boys exposed prenatally to breakdown products of certain phthalates, and these effects were similar to those seen in experiments with rats and mice exposed to phthalates.[58] A high exposure to one breakdown product of a phthalate was found to alter the development (in a laboratory culture) of human fetal testes and to reduce the number of germ cells.[59] Nevertheless, human health effects of environmental phthalate exposure have not been conclusively demonstrated. Additional research is seen as needed to confirm or refute these findings of effects at environmental levels of human exposure.

Recently, scientists have been advising that risk assessments should consider the combined effects of chemical exposures. For example, studies with rodents suggest there may be additive effects of multiple phthalate exposures.[60] A recent report issued by the National Research Council concluded that there is a need to explore the additive effects of exposure to phthalates.[61] Dr. Andreas Kortenkamp has reviewed research on the effects of mixtures of endocrine-disrupting chemicals and has called for additional, more systematic investigations of combinations of endocrine disruptors.[62]

Human hormones other than sex hormones also might be affected by environmental chemicals. A recently released study found that low-level human exposure to bisphenol A (BPA) inhibits the release of adiponectin from adipose (fat) tissue. This result indicates a possible link of BPA to

[57] Main, Katharina M., Gerda K. Mortensen, and Marko M. Kaleva, et al. 2006. Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age. Environmental Health Perspectives, v. 114, p. 270-276.

Swan, Shanna H., Katharina M. Main, and Fan Liu, et al. 2005. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environmental Health Perspectives, v. 113, n. 8, p. 1056-1061.

[58] Swan et al. 2005.

[59] Lambrot, Romain, Vincent Muczynski, and Charlotte Lecureuil, et al. 2009. Phthalates impair germ cell development in the human fetal testis in vitro without change in testosterone production. Environmental Health Perspectives, v. 117, n. 1 (January), p. 32-37.

[60] Hotchkiss, A.K., L.G. Parks-Saldutti, and J.S. Ostby, et al. 2004. A mixture of the "antiandrogens" linuron and butyl benzyl phthalate alters sexual differentiation of the male rat in a cumulative fashion. Biology of Reproduction, v. 71, p. 1852-1861.

Howdeshell, Kembra L., Vickie S. Wilson, and Johnathan Furr, et al. April 14, 2008. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague Dawley rat in a cumulative, dose additive manner. Toxicological Sciences Advance Access. Reprint received from the author.

Rider, Cynthia V., Johnathan Furr, and Vickie S. Wilson, et al. 2008, A mixture of seven antiandrogens induces reproductive malformations in rats. International Journal of Andrology, v. 31, p. 249-262.

Crofton, Kevin M., Elena S. Craft, and Joan M. Hedge, et al. 2005. Thyroid-hormone-disrupting chemicals: evidence for dose-dependent additivity or synergism. Environmental Health Perspectives, v. 113, n. 11, (November) p. 1549-1554.

[61] Committee on the Health Risks of Phthalates, National Research Council. 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. The National Academies Press, Washington DC, p. 6.

[62] Kortenkamp, Andreas. 2007. Ten years of mixing cocktails: A review of combination effects of endocrine-disrupting chemicals. Environmental Health Perspectives, v. 115, Supplement 1 (December), p. 98-105.

diabetes, because adiponectin increases insulin sensitivity and helps regulate glucose metabolism.[63] Because this study was well designed and controlled, its results are seen as particularly interesting, but until it has been replicated by an independent team of scientists, any conclusions are considered tentative.

Another chemical group that has been studied extensively is PCBs. Although the production and use of PCBs has been strictly regulated since 1976, these chemicals are ubiquitous in the air, water, soil, and many animal tissues due to their environmental persistence, tendency to bioaccumulate in animal fat, and previous widespread use. Some PCBs are known to be estrogenic.[64] In addition, PCBs may affect thyroid function,[65] and there is evidence that fetal exposure to PCBs affects cognitive development, but it is not known whether this toxicity is related to thyroid or any other type of hormone disruption.[66] In addition, some studies have found an association between human PCB exposure and low sperm counts, undescended testes, altered semen quality, lower age of onset of puberty, and shorter height at maturity.[67]

In recent years, Congress has expressed concern about the possible effects on thyroid function of perchlorate, a common pollutant in drinking water and soil. Perchlorate is formed naturally but

[63] Hugo, Eric R., Terry D. Brandebourg, and Jessica G. Woo, et al., in press, "Bisphenol A at Environmentally Relevant Doses Inhibits Adiponectin Release from Human Adipose Tissue Explants and Adipocytes," Environmental Health Perspectives, online Aug. 14, 2008, at [http://www.ehponline.org/members/2008/11537/11537.pdf].

[64] Longnecker, M.P., W.J. Rogan, and G. Lucier. 1997. 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.

Brouwer, A., U.G. Ahlborg, and F.X. van Leeuwen, et al. 1998. 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.

[65] Ibid.

Turyk, M.E., H.A. Anderson, and S. Freels, et al. 2006. Associations of organochlorines with endogenous hormones in male Great Lakes fish consumers and nonconsumers. Environmental Research, v. 102, n. 3, p. 299-307.

[66] 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. Toxicology and Industrial Health, v. 12, n. 3-4, p. 435-445.

Sagiv, Sharon K., J. Kevin Nugent, T. Berry Brazelton, et al. 2008. Prenatal Organochlorine Exposure and Measures of Behavior in Infancy Using the Neonatal Behavioral Assessment Scale (NBAS). Environmental Health Perspectives, v. 116, n. 5, p. 666-673.

Schantz, Susan L., John J. Widholm, and Deborah C. Rice. 2003. Effects of PCB exposure on neuropsychological function in children. Environmental Health Perspectives, v. 111, n. 3, p. 357-376.

Stewart, Paul, Jacqueline Reihman, and Edward Lonky, et al. 2000. Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. Neurotoxicology and Teratology, v.22, n. 1, p. 21-29.

Stewart, Paul, Susan Fitzgerald, and Jacqueline Reihman, et al. 2003. Prenatal PCB Exposure, the Corpus Callosum, and Response Inhibition. Environmental Health Perspectives, v. 111, n. 13, p. 1670-1677.

Stewart, Paul W., Edward Lonky, and Jacqueline Reihman, et al. 2008. The Relationship between Prenatal PCB Exposure and Intelligence (IQ) in 9-Year-Old Children. Environmental Health Perspectives, v. 116, n. 10, p. 1416-1422.

[67] Dhooge, Willem, Nicolas van Larebeke, and Gudrun Koppen, et al. 2006. Serum Dioxin-like Activity Is Associated with Reproductive Parameters in Young Men from the General Flemish Population. Environmental Health Perspectives, v. 114, n. 11, p. 1670-1676.

Hauser, Russ, Paige Williams, and Larisa Altshul, et al. 2005. Evidence of Interaction between Polychlorinated Biphenyls and Phthalates in Relation to Human Sperm Motility. Environmental Health Perspectives, v. 113, n. 4, p. 425-430.

also is manufactured for various products including explosives, fireworks, road flares, and solid rocket fuel and often is associated in the environment with sites operated by the Department of Defense. Perchlorate is known to disrupt the uptake of iodine by the thyroid, and health effects associated with perchlorate exposure are expected to parallel those caused by iodine deficiency. Iodine deficiency decreases the production of thyroid hormones, which help regulate the body's metabolism and growth. A key concern is that impairment of thyroid function in pregnant women can affect brain development in fetuses and nursing infants and can lead to attention deficit disorder, generally delayed development, and decreased learning capacity.[68] Several studies have found that at significantly higher levels of perchlorate exposure than the amounts typically observed in the environment, thyroid changes occur in humans.[69] However, a 2006 study by the Centers for Disease Control and Prevention (CDC) of a representative sample of the general U.S. population found that environmental exposures to perchlorate have an effect on thyroid hormone levels in women who are deficient in iodine (and on levels of the pituitary gland's thyroid stimulating hormone in all women). (No effect was found in men.) Fully 36% of the 1,111 women in this study were found to be iodine deficient.[70] [71]

Animal Studies

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.[72]

Fish

Feminization of male fish due to exposure to endocrine disrupting chemicals in the environment is an increasing concern.[73] Fish appear to be useful as sentinels for the presence and possible hazard of endocrine disrupting chemicals in the aquatic environment, since they are currently the only vertebrates for which the connection between environmental contamination and adverse effects on health has been established in both field[74] and laboratory[75] studies. In addition, fish are

[68] Zoeller, R. Thomas, Amy L.S. Dowling, and Carolyn T.A. Herzig, et al. 2002. Thyroid hormone, brain development, and the environment. Environmental Health Perspectives, v. 110, Supp. 3, p. 355-361.

[69] Kelsh, Michael A., Patricia A. Buffler, and Jorge J. Daaboul, et al. 2003. Primary congenital hypothyroidism, newborn thyroid function, and environmental perchlorate exposure among residents of a southern California community. Journal of Occupational Environmental Medicine, v. 45, n. 10, p. 1116-1127.

[70] Blount, Benjamin C., James L. Pirkle, and John D. Osterloh, et al. 2006. Urinary Perchlorate and Thyroid Hormone Levels in Adolescent and Adult Men and Women Living in the United States," Centers for Disease Control and Prevention, in Environmental Health Perspectives, v. 114, n. 12, p. 1865-1871.

[71] For more information about perchlorate, see CRS Report RS21961, *Perchlorate Contamination of Drinking Water: Regulatory Issues and Legislative Actions*, by Mary Tiemann.

[72] Jobling, Susan, Monique Nolan, and Charles R. Tyler, et al. 1998. "Widespread sexual disruption in wild fish," Environmental Science and Technology, v. 32, n. 17, p. 2498-2506.

[73] However, feminization and any resulting effects on fish populations are not the only concerns. Another potential effect might be immune system changes and perhaps greater susceptibility to infections and other diseases. It was fish kills and skin lesions on a number of fish species in the South Branch of the Potomac River that prompted the Blazer et al. (2007) study of smallmouth bass which is described below.

[74] Folmar, Leroy C., George R. Gardner, and Martin P. Schreibman, et al. 2001. Vitellogenin-induced pathology in male summer flounder (Paralichthys dentatus). Aquatic Toxicology, v. 51, p. 431-441.

Folmar, Leroy C., Nancy D. Denslow, and Vijayasri Rao, et al. 1996. Vitellogenin introduction and reduced serum testosterone concentrations in feral male carp (Cyprinus carpio) captured near a major metropolitan sewage treatment (continued...)

exposed to any contaminants in their aquatic habitats through skin absorption, food ingestion, and dissolved gas absorption across the gills. Aquatic food chains often are long, relative to terrestrial food chains, so bioaccumulation potential may be greater. 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.

Feminization of male fish collected from British rivers near the effluent from wastewater treatment plants alerted the scientific community to the potential hazard of endocrine disrupting chemicals (specifically, synthetic female hormones) in the environment.[76] Feminization of males was confirmed by the presence of eggs in the testes and vitellogenin (a protein in the yolk of 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 ability to reproduce.) More recently, marine fish populations in the English Channel and in Tokyo Bay have shown evidence of feminization.[77]

In the United States, studies have found feminized male fish in diverse locations. For example, there is a report of complete sex reversal of male salmon in the state of Washington.[78] Others have reported intersex trout in Rocky Mountain National Park and Glacier Park,[79] hornyhead turbot in southern California,[80] and white sucker in Boulder Colorado.[81]

In spring of 2004, scientists found a high prevalence of feminized smallmouth bass in the South Branch of the Potomac River, which drains a rural area of West Virginia.[82] Water samples in the area detected a number of known endocrine disruptors with estrogenic activity including several pesticides, a degradation product of industrial phenols, and two polybrominated diphenyl ethers

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plant. Environmental Health Perspectives, v. 104, p. 1096-1100.

Harries, J.E., D.A. Sheahan, and S. Jobling, et al. 1997. Estrogenic activity in five United Kingdom rivers detected by measurement of vitellogenesis in caged male trout. Environmental Toxicology and Chemistry, v. 16, p. 534-542.

Jobling, Susan, Monique Nolan, and Charles R. Tyler, et al. 1998. Widespread sexual disruption in wild fish. Environmental Science and Technology, v. 32, p. 2498-2506.

[75] 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.

[76] Jobling, Susan, Monique Nolan, and Charles R. Tyler, et al. 1998. Widespread sexual disruption in wild fish. Environmental Science and Technology, v. 32, n. 17, p. 2498-2506.

[77] Gross-Sorokin M.Y., S.D. Roast, and G.C. Brighty. 2006. Assessment of feminization of male fish in English rivers by the Environment Agency of England and Wales. Environmental Health Perspectives, v. 114 (Supplement 1), p. 147-151.

[78] James J. Nagler, Jerry Bouma, and Gary H. Thorgaard, 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.

[79] National Park Service. News release, Feb. 26, 2008. "Airborne contaminants study released: Measurable levels detected in twenty western U.S. and Alaska National Parks." p. 2.

[80] Renner, Rebecca. 2009. Sex-changing fish: caused by contamination or nature? Environmental Science & Technology, Article ASAP, Publication Date (Web): January 14, 2009, [http://pubs.acs.org/doi/abs/10.1021/es8036912], visited Jan. 21, 2009.

[81] Vajda, Alan, Larry Barber, and James L. Gray, et al. 2008. Reproductive disruption in fish downstream from an estrogenic wastewater effluent. Environmental Science & Technology, v. 42, n. 9, p. 3407–3414.

[82] Blazer, V.S., L.R. Iwanowicz, and D.D. Iwanowicz, et al. 2007. Intersex (testicular oocytes) in smallmouth bass from the Potomac River and selected nearby drainages. Journal of Aquatic Animal Health, v. 19, p. 242-253.

(PBDEs), but the study authors concluded that a combination of contaminants probably was responsible for the observed effects on fish.[83] Recent research has demonstrated that mixtures of estrogenic chemicals can act in combination, exerting adverse effects on fish even when each component is present at a level below the threshold level for producing such effects.[84] Fish were also taken from several other rural sites in West Virginia that were characterized by low human population and low intensity agriculture. At these sites scientists found a lower prevalence of feminized bass.[85] In contrast, in a more heavily populated and more intensely agricultural part of Virginia, 80 to 100% of male bass taken from the Shenandoah River were feminized.[86] The cellular responses to ethynylestradiol (the bioactive component of contraceptive pills) that lead to feminization have been documented.[87]

Androgenic substances (i.e., substances with an effect similar to that of male sex hormones) also have been detected in environmental samples, especially in pulp mill effluents, and studies have linked such effluents to masculinized female fish.[88] Although both androgenic and estrogenic effects have been observed in fish, estrogenic activity appears to be more ubiquitous and hence better studied.[89] Moreover, the presence of estrogenic substances in some U.S. rivers and streams, especially near outfalls from wastewater treatment plants, has been well documented.[90]

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[83] Ibid., p. 250.

[84] Brian, Jayne V., Catherine A. Harris, and Martin Scholze, et al. 2007. Evidence of estrogenic mixture effects on the reproductive performance of fish. Environmental Science & Technology, v. 41, n. 1, p. 337-344.

[85] Ibid.

[86] Ibid.

[87] Filby, A.L., K.L. Thorpe, G. Maack and C.R. Tyler. 2007. Gene expression profiles revealing the mechanisms of anti-androgen- and estrogen-induced feminization in fish. Aquat. Toxicol. 81(2):219-231.

[88] Larsson, D.G., M. Adolfsson-Erici, and P. Thomas. 2006. Characterization of putative ligands for a fish gonadal androgen receptor in a pulp mill effluent. Environmental Toxicology and Chemistry, v. 25, n. 2 (Feb.), p.419-427.

Galloway, Brendan, K.R. Munkittrick, and S. Currie, 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.

Larsson, D.G.J., H. Hallman, and L. Forlin. 2000. More male embryos near a pulp mill. Environmental Toxicology and Chemistry, v. 19, n. 12, p. 2911-2918.

Munkittrick, Kelly R., M.E. McMaster, and M.R. Servos, et al. 2000. 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 (1999), (ed. Bergitta Norberg), Bergen, Norway.

[89] 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, K. Lundstedt-Enkel, and K.H. Olsen, et al. 2000. Estrogen in food or water severely [a]ffect the male goldfish (Carassius auratus) sexual behavior. In: 6th International Symposium on the Reproductive Physiology of Fish (1999), (ed. Bergitta Norberg), Bergen, Norway.

Jobling, Susan, D. Sheahan, and J.A. Osborne, 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.

Nash, J.P., D.E. Kime, and L.T. Van der Ven, et al. 2004. Long-term exposure to environmental concentrations of the pharmaceutical ethynylestradiol causes reproductive failure in fish. Environmental Health Perspectives, v. 112, n. 17, p. 1725-1733.

Kramer, V.J., S. Miles-Richardson, and S.L. Pierens, et al. 1998. Reproductive impairment and induction of alkaline-labile phosphate, a biomarker of estrogen exposure, in fathead minnows (Pimephales promelas) exposed to waterborne 17b-estradiol. Aquatic Toxicology, v. 40, p. 335-360.

Matthiessen, P. 1998. Effects on fish of estrogenic substances in English rivers. In: Principles and Processes for (continued...)

The significance of the numerous observations of feminized male fish for the sustainability of wild populations was unknown until recently. The results of a study in the Experimental Lakes Area of northwestern Ontario, Canada, demonstrated that sustainability might be adversely affected by endocrine-disrupting chemicals. Chronic exposure of fathead minnow in one lake to low concentrations[91] of the potent synthetic estrogen 17α-ethynylestradiol (EE2) nearly extinguished this population after only two years.[92] EE2, which is the most common component of birth control pills, is often found in wastewater plant effluent and has been found in U.S. surface water at concentrations ranging from 0.1 to 5.1 ng/l.[93] Academic scientists working together with pharmaceutical company scientists have derived a predicted no-effect concentration for EE2 of 0.35 ng/l for aquatic life in general.[94]

Other Wild Vertebrates

Reproductive or developmental problems potentially resulting from hormone exposure have been observed in other wild vertebrate species, especially fish-eating species, including birds (such as gulls, terns, ospreys, eagles, and pelicans), polar bears,[95] Florida panthers,[96] alligators,[97] river otters,[98] and mink.[99] In addition, there is growing evidence for effects of environmental exposure to endocrine disruptors in marine mammals.[100] The accumulation of persistent chlorinated organic

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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.

[90] Campbell, Chris G., Sharon E. Borglin, and F.Bailey Green, et al. 2006. Biologically directed environmental monitoring, fate, and transport of estrogenic endocrine disrupting compounds in water: A review. Chemosphere, v. 65, p.1265-1280.

[91] The concentrations were 5-6 nanograms of EE2 per liter of water (ng/l), which also may be expressed as 5-6 parts per trillion (ppt).

[92] Kidd, Karen, A., Paul J. Blanchfield, and Kenneth H. Mills, et al. 2007. Collapse of a fish population after exposure to a synthetic estrogen. Proceedings of the National Academy of Sciences, v. 104, n. 21, p. 8897-8901.

[93] Campbell et al. op cit.

[94] Caldwell, Daniel J., Frank Mastrocco, and Thomas H. Hutchinson, et al. 2008. Derivation of an aquatic predicted no-effect concentration for the synthetic hormone, 17α-ethinyl estradiol. Environmental Science & Technology, v. 42, p. 7046-7054.

[95] Braathen, Marte, Andrew E. Derocher, and Oystein Wiig, et al. 2004. Relationships between PCBs and thyroid hormones and retinol in female and male polar bears. Environmental Health Perspectives, v. 112, n. 8, p. 826-833.

[96] 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.

[97] Guillette, Louis J., Timothy S. Gross, and Denise A. Gross, et al. 1995. Gonadal steroidogenesis in vitro from juvenile alligators obtained from contaminated or control lakes," Environmental Health Perspectives, v. 103, n. 4, p. 31-36.

[98] Grove, R.A., and C.J. Henny. 2008, Environmental contaminants in male river otters from Oregon and Washington, USA, 1994-1999. Environmental Monitoring and Assessment, v. 145, p. 49-73.

[99] 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.

[100] 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.

chemicals, such as PCBs, in seals and dolphins has been well documented,[101] and research indicates that the thyroid hormone system in harbor seals is "highly sensitive to disruption by environmental contaminants," particularly by PCBs.[102] Laboratory studies of a beluga whale protein that is key in many endocrine disrupting effects (the aryl hydrocarbon receptor) reveal that the protein binds strongly to dioxins and PCBs. This may increase the likelihood that toxic responses can be elicited by contaminants in the environment.[103]

However, as is the case with humans, cause-and-effect relationships are difficult (or impossible) to show experimentally for marine mammals, because direct toxicity testing is precluded by logistical, legal, and ethical constraints.

Invertebrates

There is evidence of endocrine effects in some marine invertebrates. Ambiguous genitalia have been found by the EPA in Maine bivalves, allegedly due to herbicides.[104] 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.

Laboratory Rodents

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 effects that would impair fertility in every exposed mouse, but in no unexposed mouse.[105] In addition, uterine cancer occurred in about one-third of the exposed mice, but not in

[101] Watanabe, M., K. Kannan, and 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, and 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.

[102] Tabuchi, Maki, Nik Veldhoen, and Neil Dangerfield, et al. 2006. PCB-related alteration of thyroid hormones and thyroid hormone receptor gene expression in free-ranging harbor seals (Phoca vitulina). Environmental Health Perspectives, v. 114, n. 7, p. 1024-1031.

[103] 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, n. 1, p. 41-56.

[104] Van Beneden, R.J., G.R. Gardner, and N.J. Blake, 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.

[105] Newbold, R.R., E.P. Banks, and B. Bullock, et al. 2001. Uterine adenocarcinoma in mice treated neonatally with (continued...)

the unexposed mice.[106] (An expert panel of the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction found in 2006 that the results of rodent studies were sufficient to conclude that genistein produces reproductive and developmental toxicity in offspring of rodents,[107] but another expert panel report concluded that evidence was insufficient to demonstrate that soy formula would or would not produce such effects.[108])

Some on-going studies of developmental effects in rats have found effects on the reproductive organs from very low levels of exposure to DES, bisphenol-A, an ingredient in some plastic, and other substances.[109] Other studies found no effects.[110] The resulting controversy has prompted some scientists to note that the design of laboratory studies often has contributed to the confusion, because statistical measures were not employed to ensure adequate power to detect subtle effects.[111] In 2001, an expert workshop to evaluate the data on low-dose effects of endocrine disruptors concluded that biological effects have been shown to occur following exposure to some estrogenic compounds at very low levels.[112] The question remains whether those effects would adversely affect rodent health, however.[113]

Environmental Exposure to Potential Endocrine Disruptors

Concern about possible human or wildlife hormone disruption has been fueled by the limited information that is available about levels of potential hormone disruptors in the environment. It is known, however, that some potential endocrine disruptors are heavily used and, in some cases, released to the environment. For example, pesticides such as DDT and dieldrin, now banned, still are found in many rivers and streams.[114] Wastewater effluent from sewage treatment plants contains many potential endocrine disruptors, including synthetic (pharmaceutical) hormones.[115]

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genistein. Cancer Research, v. 61, n. 11, p. 4325-4328.

[106] Ibid.

[107] U.S. Department of Health and Human Services, National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction. 2006. NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Genistein. NTP-CERHR-GENISTEIN-06.

[108] National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction. 2006. NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Soy Formula. NTP-CERHR-SOY FORMULA-06.

[109] U.S. Department of Health and Human Services (HHS), National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction, "NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A," NIH Publication No. 08-5994, September 2008, 321pp, at

[http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.pdf].

[110] Ibid.

[111] Scholze, Martin, and Andreas Kortenkamp. 2007. Statistical power considerations show the endocrine disruptor low-dose issue in a new light. Environmental Health Perspectives, v. 115, Supp. 1, p. 84-90.

[112] National Toxicology Program's Report of the Endocrine Disruptors Low Dose Peer Review. (2001) National Toxicology Program, U.S. Department of Health and Human Services, [http://ntp-server.niehs.nih.gov/htdocs/liason/LowDoseWebPage.html]

[113] 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.

[114] National Park Service. News release, Feb. 26, 2008. "Airborne contaminants study released: Measurable levels detected in twenty western U.S. and Alaska National Parks." p. 2.

[115] Liney, Katherine E., Josephine A. Hagger, and Charles R. Tyler, et al. 2006. Health effects in fish of long-term (continued...)

The U.S. Geological Survey has found synthetic hormones in U.S. streams.[116] Concentrated animal feeding lots are another potential source of environmental contamination.[117] Other potential endocrine disruptors are prevalent in certain foods, such as soy-based milk substitutes, because soy beans contain phytoestrogens (i.e., isoflavonoids such as genistein) at relatively high levels.[118] 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.[119] Others say 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.

Data collected during the National Health and Nutrition Examination Survey indicates that most people in the United States are exposed to various potential endocrine disruptors that are in widespread use. Bisphenol A was detected in more than 90% of the surveyed population.[120] In addition, the survey found almost universal American exposure to low levels of the most common phthalates, usually multiple phthalates.[121] Women tend to have greater exposure than men, but children appear to be the group most exposed to di-(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and benzyl butyl phthalate (BBP). Studies of amniotic fluid have also documented exposure to multiple phthalates for human fetuses.[122] More generally, babies may be the most heavily exposed group.[123] Children may be exposed to such chemicals through their mothers' blood prenatally, through breast milk, or by eating certain foods.[124]

Release of a chemical to the environment and even proof of exposure to the chemical do not necessarily lead to toxic effects, even for vulnerable populations of animals or people. Some

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exposure to effluents from wastewater treatment works. Environmental Health Perspectives, v. 114, Supp. 1, p. 81-89.

EPA. Expanded investigations of pharmaceuticals in fish tissue, [http://www.epa.gov/waterscience/ppcp/studies/fish-expand.html].

[116] Kolpin, Dana W., Edward T. Furlong, and Michael T. Meyer, et al. 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. Environmental Science & Technology, v. 36, n. 6, p. 1202-1211.

[117] Durhan, Elizabeth J., Christy S. Lambright, and Elizabeth A. Makynen, et al. 2006. Identification of metabolites of trenbolone acetate in androgenic runoff from a beef feedlot. Environmental Health Perspectives, v. 114, Supp. 1, p. 65-68.

[118] The isoflavonoids appear to exert both estrogenic and anti-estrogenic effects which are not completely understood.

[119] Easterbrook, Gregg. 1999. Another phony health scare. Science fiction. New Republic, v. 221, Aug. 30, 1999, p. 20-22.

[120] For more information about bisphenol A, see CRS Report RS22869, *Bisphenol A (BPA) in Plastics and Possible Human Health Effects*, by Linda-Jo Schierow and Sarah A. Lister.

[121] Ibid.

[122] Silva, M.J., J.A. Reidy, and A.R. Herbert, et al. 2004. Detection of phthalate metabolites in human amniotic fluid. Bulletin of Environmental Contamination and Toxicology, v. 72, p. 1226-1231.

[123] Wormuth, Matthias, Martin Scheringer, and Meret Vollenweider, et al. 2006. What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? Risk Analysis, v. 26, n. 3, p. 803-824.

[124] For more information about phthalates, see CRS Report RL34572, *Phthalates in Plastics and Possible Human Health Effects*, by Linda-Jo Schierow and Margaret Mikyung Lee.

believe that available data are reassuring, because known potential disruptors of endocrine function generally are present in the environment at very low levels.[125]

On the other hand, there are no measurements at all of environmental concentrations for most chemicals in the environment, some of which might be affecting hormones. Some known hormone disruptors, such as phthalates or bisphenol A, are ubiquitous at low levels, raising the question of long-term effects and possible additive or synergistic effects with continual exposure.[126] Of particular concern are chemicals designed to be biologically active in humans or in pests that are 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. Other chemicals, such as PCBs and some dioxins, are persistent in the environment and are known to bioconcentrate in the food chain.

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 in 1999 –

> 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.[127]

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

[125] Scientists disagree about whether it is likely that animals or people would experience adverse effects of exposure to very low doses of chemicals with the potential to disrupt endocrine function. Detailed arguments for and against the hypothesis of low-dose effects are provided in Richter, C.A., et al. 2007, In vivo effects of bisphenol A in laboratory rodent studies, Reproductive Toxicology, v. 24, n. 2, p. 199-224; and Willhite, C.C., et al., 2008, Derivation of a bisphenol A oral reference dose (RfD) and drinking-water equivalent concentration, Journal of Toxicology and Environmental Health, Part B, Critical Reviews, v. 11, n. 2, p. 69-146.

[126] 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.

[127] National Academy of Sciences, op cit., p. 7.

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.[128] On January 19, 2001, EPA and NRDC agreed to settle the lawsuit. The settlement agreement states that endocrine disruptor screening would begin no later than spring 2004.[129] That did not occur.

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. Several test protocols approved for use in the screening program have been inadequately validated, according to these stakeholders. Since chemical producers would conduct the actual screening of chemicals, they want to ensure that screening requirements established by EPA would 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: Would 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 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 inspection of internal 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.

[128] *Natural Resources Defense Council v. U.S. Environmental Protection Agency*, No. C993701CAL, Jan. 19, 2001.

[129] Ibid.

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. Others contend that animal models provide valuable information about the potential human health effects of chemical exposure, and animal welfare is protected by laboratory guidelines for their care. Alternative test methods for many kinds of effects have not been developed, it is argued.

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 103rd 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" (P.L. 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 106th Congress made ICCVAM a permanent interagency coordinating committee (P.L. 106-545). EPA is a member of this committee.

Regulation of Endocrine Disruptors

If EPA determines through the endocrine disruptor screening program or some other program that a chemical poses a risk to public health due to its effects on endocrine systems, the agency is authorized to act under its existing legal authorities. The authorities available to EPA that are likely to be most relevant to the protection of public health from toxic chemicals derive primarily from the Safe Drinking Water Act, the Federal Water Pollution Control Act, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and the Toxic Substances Control Act.[130] Alternatively, EPA may refer a substance to another agency for action. For example, EPA might suggest that the Food and Drug Administration or the Occupational Safety and Health Administration regulate the use of particular chemicals to reduce risks.

Because many chemicals that may be endocrine disruptors have a variety of uses and may be released to the environment at several stages in their lifecycles, multiple agencies are likely to have a stake in their regulation. In such cases, any overlapping or inconsistent risk assessments, guidelines, or regulations are likely to spark controversies. For example, EPA and FDA at one time published risk assessments for mercury and guidance for consumers of fish containing

[130] For brief summaries of these laws, see CRS Report RL30030, *Clean Water Act: A Summary of the Law*, by Claudia Copeland; CRS Report RL31921, *Pesticide Law: A Summary of the Statutes*, by Linda-Jo Schierow; CRS Report RL31243, *Safe Drinking Water Act (SDWA): A Summary of the Act and Its Major Requirements*, by Mary Tiemann; and CRS Report RL31905, *The Toxic Substances Control Act (TSCA): A Summary of the Act and Its Major Requirements*, by Linda-Jo Schierow. These and other environmental laws also are summarized in CRS Report RL30798, *Environmental Laws: Summaries of Major Statutes Administered by the Environmental Protection Agency (EPA)*, by Susan R. Fletcher et al.

mercury that appeared to be inconsistent. The resulting controversy was quelled only when the two agencies issued a joint communication. Some in Congress might be expected to urge coordination of agency efforts to avoid such controversies. Cooperation among agencies also might lead to more cost-effective regulation, an objective of President Obama and many Members of Congress.

Another concern due to multiple uses and releases of chemicals and divided authorities for regulating them might be that risks could be under-estimated and thus under-regulated if they were assessed for each source of exposure and each exposed population individually, rather than aggregated from all sources, combined with risks from chemicals with similar effects, and calculated cumulatively over time. This is a particular concern when the health effects of exposure are not immediate or not obvious, as might be the case for certain reproductive or developmental effects. This situation arguably occurred with respect to phthalates: it was the cumulative risk assessment conducted by the interagency National Toxicology Program that caused scientists to express concern about possible consequences of exposure to phthalates from multiple sources for infants and fetuses. Scientists' concern prompted Congress to require action by regulatory agencies.

Congress might wish to evaluate whether agencies are adequately assessing cumulative and aggregate risks. Various groups of scientists have called for increased use of cumulative risk assessments.[131] Congress has acted in the past to require cumulative and aggregate risk assessments for pesticides, when it enacted the FQPA. The Kid-Safe Chemicals Act (H.R. 6100/S. 3040) in the 110th Congress would have extended that requirement to other chemicals.

The nature of endocrine disruption may challenge would-be regulators. Disruption may consist of enhancement or inhibition of effects that vary widely within populations of humans and wildlife. Under some circumstances, disruption of a hormonally regulated process even may be beneficial. Moreover, endocrine disruption may not fit the traditional model of the relationship between increasing chemical exposure and effects, and effects may vary depending on the timing of exposure and other factors. Early indicators of endocrine disruption may not be considered adverse. At what point might regulators intervene, and under what authority? Some laws might require substantial evidence of severe effects prior to agency action, while others might authorize action when risks are less certain. Congress may consider whether statutes provide agencies with appropriate authority and directives for regulating endocrine disrupting chemicals.

Congress might also consider whether agency budgets are adequate to support appropriate levels of research and regulatory activity. Within the context of the overall federal budget, funding for research, chemical screening programs, and regulatory activity, in the view of some, should be proportionate to congressional concern about the potential risks to human or animal health posed by endocrine disruptors.

[131] Committee on Improving Risk Analysis Approaches Used by the U.S. EPA, National Research Council of the National Academies. 2008. Science and Decisions: Advancing Risk Assessment. Prepublication Copy. Washington DC: The National Academies Press. p.9.

Committee on the Health Risks of Phthalates, National Research Council of the National Academies. 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. Washington, DC: The National Academies Press. 142 p.

Conclusion

Chemicals with the potential to disrupt endocrine systems are frequently present in the environment, particularly in rivers and streams, and in some consumer products. Exposure to high levels of some of these chemicals has been shown to harm insects, some vertebrate wildlife, and aquatic life by affecting reproductive and other hormone-dependent processes. In controlled laboratory experiments, some scientists have found that relatively low levels of certain chemicals harm the endocrine systems of fish and wildlife, particularly when exposure is continuous, chemicals bioaccumulate, or animals are exposed simultaneously to several chemicals with similar effects. Fish studies provide the most compelling evidence that endocrine disruption might be occurring due to environmental exposures to contaminants. Reproductive or developmental problems potentially resulting from hormone exposure also have been observed in birds, polar bears, Florida panthers, alligators, river otters, mink, and marine invertebrates.

Some scientists have hypothesized that existing environmental levels of chemical pollutants might be harming human health by disrupting endocrine functions. They point to increased rates of certain human health problems, demonstrated harm to human endocrine systems when people have been exposed to high levels of certain chemicals, and epidemiologic studies that have found statistical associations between exposure to environmental levels of potential endocrine disruptors and diabetes, malformations, sexual function, cognitive development, thyroid function, and other potentially hormone-mediated effects. The environmental endocrine disruptor hypothesis is disparaged by other scientists, because known potential disruptors of endocrine function generally are present in the environment at very low levels, especially compared to the levels of hormones that are naturally present in the human body, as well as in some of the plants that humans eat. Many scientists who are not convinced there is an environmental problem nonetheless are concerned about the issue, because there are no measurements at all of environmental concentrations for most chemicals, people are known to be exposed to low levels of multiple environmental contaminants with endocrine-disrupting potential for which potential cumulative effects have not been assessed, and some studies suggest the public health consequences of exposure might be significant.

Congress might be asked to consider various issues connected to the endocrine disruptor hypothesis. In 1996, Congress mandated chemical screening for endocrine-disrupting potential. The screening program has not yet been launched, and some argue that it should not be launched until the complete test battery is validated. Others are concerned about the extent to which EPA might rely on animal experimentation in its screening program. Once the program is implemented, Congress might consider whether statutes and regulations provide adequate authority and direction with respect to the influence of any findings of endocrine disruption on the regulation of specific chemicals, chemical groups, uses, or products.

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