In 1996, the US Congress mandated that the US Environmental Protection Agency (EPA) create and regulate the Endocrine Disruptor Screening Program. The program tests industrial and agricultural chemicals for hormonal impacts in humans and in wildlife that may disrupt organisms' endocrine systems. The endocrine system regulates the release of small amounts of chemical substances called hormones to keep the body functioning normally. Some chemicals can impede the endocrine system's function by mimicking or blocking hormone reception, which can disrupt processes of development and reproduction and harm organisms. As of 2017, the Endocrine Disruptor Screening Program is the largest US program to identify and regulate chemicals that affect the normal production of sex hormones like estrogen and androgen, which can have long-term effects on development and reproduction.

Scientists had studied how chemicals affected reproduction for decades before Rachel Carson, in 1962, published her book *Silent Spring*, an account of how agricultural and industrial chemicals affect ecosystems. Environmental historian Linda J. Lear later credited Carson's book with ushering in a new environmental movement in the US, for which the Endocrine Screening Disruptor Program was one of the many results. By the 1970s, the US Food and Drug Administration (FDA), headquartered in Silver Spring, Maryland, had banned several chemicals, including the insecticide dichloro-diphenyl-trichloroethane (DDT), widely used in the early 1900s to combat insect-borne diseases like malaria and typhus, before being labeled a human carcinogen. However, as scientists synthesized new chemicals for industrial and agricultural uses, even more regulatory issues were raised.

In response to those regulatory issues, environmental health analyst Theo Colborn convened the Wingspread Conference in 1991 in Racine, Wisconsin, to address the environmental effect of manufactured chemicals. The attendees at Wingspread coined the term 'endocrine disruptor' to describe the effects of an increasing number of chemicals that pose a threat to wildlife and human health by disrupting the function of the endocrine system, including in the processes of development and reproduction in animals. The scientists also drew links between effects observed in wildlife and those seen in humans, like the drug diethylstilbestrol, which doctors prescribed to women to prevent miscarriages but which later caused reproductive cancers.
The meeting manuscript from the Wingspread Conference, "Chemically Induced Alterations in Sexual and Functional Development: the Wildlife/Human Connection," was published in 1992, and then again in a highly cited 1993 paper, "Developmental Effects of Endocrine Disrupting Chemicals in Wildlife and Humans." However, both of those publications were directed at the scientific community. Endocrine disruptors did not receive widespread public attention until 1996, when Colborn and colleagues published the book *Our Stolen Future: Are we Threatening our Fertility, Intelligence, and Survival? A Scientific Detective Story*, detailing the possible effects of endocrine disruptors on human health for a general audience.

The Wingspread Conference and the publication of Colborn's book, as well as the scientific community's growing support of the endocrine disruptor theory, pressured the US government to act. Prior to 1996, the EPA, headquartered in Washington, D.C., regulated pesticides through two legislative acts. The Food, Drug, and Cosmetic Act of 1938 mandated that the US federal government establish maximum legal limits of pesticides allowed in food. The Federal Insecticide, Fungicide, and Rodenticide Act of 1947 required the government to register all pesticides used in the US, and to regulate the warning labels that appear on those products to reduce risks to humans [3] and to the environment. After US President Richard Nixon established the EPA in 1970, it began to enforce those laws.

In 1996, US Congress passed the Food Quality Protection Act and amendments to the Safe Water Drinking Act, both of which President Bill Clinton signed into law. Those acts expanded the EPA's responsibility to regulate pesticides, specifically endocrine disruptors. The Food Quality Protection Act required the EPA to create a health-based standard for pesticides in food with special considerations for the health of infants and children. The act also mandated that the EPA expedite the approval process for pesticides, create incentives for the development of new crop protection tools, and regularly re-evaluate pesticides as a requirement of continued government approval. The amendments to the Safe Water Drinking Act required the EPA to use science-based standards and risk assessments to ensure the safety of public water systems. Both of those acts specifically charged the EPA with the screening of pesticides for endocrine disruptors that mimic estrogen [7], a female sex hormone [5].

As a result of the 1996 acts that expanded the EPA's regulatory requirements, the EPA created the Endocrine Disruptor Screening and Testing Advisory Committee that same year to write a report on the proper regulatory mechanism for endocrine disruptors. In 1998, the committee released its report, urging the EPA to expand screening to include commercial chemicals, environmental contaminants, cosmetics, and other substances. The committee further urged screenings to include endocrine disrupting effects of chemicals mimicking male sex hormones [8] and thyroid chemicals, as well as the environmental effects of those chemicals. The report then suggested a two-tiered screening program to determine the effects of those chemicals on humans [3] and on wildlife.

The EPA spent nearly a decade creating the initial list of chemicals to be tested and the tests that would be used to screen for those chemicals. In 2005, the EPA asked for public input online, as mandated by federal law, to generate both the list of chemicals and the appropriate screening tests. By 2007, the EPA drafted a list of chemicals based on that public feedback, and in 2009 the EPA announced the initial list of sixty-seven chemicals to be tested. The same year, the EPA exempted some chemicals and other substances not expected to cause an endocrine response. In 2010, the EPA released a second list of chemicals and required
producers to demonstrate their safety in order to garner EPA approval. The list was revised in 2013.

The first tier of the two-tiered screening program required the manufacturer of a chemical to identify the chemical's interactions with estrogen, androgen, and thyroid signaling pathways. Tier 1 used eleven different chemical tests, or assays: six conducted in live organisms like rats or mice, and five using in vitro tests in the laboratory. To ensure that a risky and potentially harmful chemical did not escape testing, researchers designed Tier 1 tests to minimize the chances that they falsely indicated chemicals as not interacting with those pathways (false negatives). As a result, some harmless chemicals were labeled as harmful and sent to Tier 2 testing, where scientists further determined if they actually posed a threat. In the second tier of testing, scientists scrutinized all chemicals flagged during Tier 1 testing for endocrine disruption. The second tier aimed to identify the adverse effects caused by those compounds that showed some kind of interaction in Tier 1 tests. Tier 2 tests also attempted to generate dose-response data, which indicated the amount of that chemical to which an animal needed to be exposed to cause the endocrine disruption seen in Tier 1 testing.

Some people critiqued the Endocrine Disruptor Screening Program for its testing methods to screen potentially harmful chemicals. Within the field of toxicology, researchers often assumed that the higher the dose of toxin, the more extreme the observed response will be, a relationship that produces a linear dose-response curve. However, researchers showed that endocrine disruptors do not produce linear dose-response curves. Instead, many endocrine disruptors present a U-shaped dose-response curve, with the most severe effects caused by substances at either extremely low doses or extremely high doses. Conversely, other endocrine disruptors present upside-down U-shaped dose-response curves, for which the most extreme responses occur at intermediate doses and relatively little response occur at extremely high or extremely low doses. Critics of the tests used by the Endocrine Disruptor Screening Program noted that while several different dose levels will determine whether or not a given substance interacts with the endocrine system, researchers often assumed that the dose response curves were linear, and didn't test enough dose levels to determine the actual dose-response curve.

Toxicologists further critiqued the Endocrine Disruptor Screening Program because the tests failed to indicate the effects of chemicals across multiple life stages. They said such tests were needed because hormone regulation changes throughout prenatal development and into adulthood. Endocrine disruptors often mimic, or block reception of, hormones normally found in the body. Hormones elicit responses at very low levels, parts per billion, so little is needed to disrupt the system, especially during early development, when a small change can permanently affect the organism.

Some people also argued that the screening program lacked specificity, as the same eleven tests were used to determine the toxicity of any chemical or substance. Chemical manufacturers also criticized the tests' high false positive rates, as manufacturers must fund the tests, even when a chemical is inadvertently labeled in Tier 1 as potentially dangerous but Tier 2 tests indicate no measurable effects. In the early decades of the twenty-first century, manufacturers payed approximately $860,000 to get one chemical through Tier 1 testing, and they incurred additional costs if the chemical must go to Tier 2 testing. Regardless, the EPA's Endocrine Disruptor Screening Program was the only program in the US with the goal of identifying chemicals and substances that directly interact with the hormone system in the
Sources

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