A Biography of Endocrine Disruptors:

The Narrative Surrounding the Appearance and

Regulation of a New Category of Toxic Substances

by

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ABSTRACT

Endocrine disruptors are chemicals that interact with the hormone system to negative effect. They 'disrupt' normal processes to cause diseases like vaginal cancer and obesity, reproductive issues like t-shaped uteri and infertility, and developmental abnormalities like spina bifida and cleft palate. These chemicals are ubiquitous in our daily lives, components in everything from toothpaste to microwave popcorn to plastic water bottles. My dissertation looks at the history, science, and regulation of these impactful substances in order to answer the question of how endocrine disruptors appeared, got interpreted by different groups, and what role science played in the process. My analysis reveals that endocrine disruptors followed a unique science policy trajectory in the US, rapidly going from their proposal in 1991 to their federal regulation in 1996, even amid intense and majority scientific disagreement over whether the substances existed at all. That trajectory resulted from the work of a small number of scientist-activists who constructed a concept and category as scientific, social, and regulatory. By playing actors from each sphere against each other and advancing a very specific scientific narrative that fit into a regulatory and social window of opportunity in the 1990s, those scientist-activists made endocrine disruptors a national issue that few could ignore. Those actions resulted in the Endocrine Disruptor Screening Program, a heavily-criticized and ineffective regulatory program. My dissertation tells a story of the past that informs the present. In 2018, the work of researchers, public media, and policymakers in the 1990s continues to play out, evident in the deep scientific division over endocrine disrupting effects and the inability of the European Union to settle on even a definition of endocrine disruptors for regulation purposes.

TABLE OF CONTENTS

CHAPTER Page

CHAPTER Page

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

INTRODUCTION

Endocrine disruptors are not well known in the US in 2018. Over the last four years, I have expended a tremendous amount of time and breath explaining my dissertation topic to people who quickly become interested (and a bit terrified) when I explain. The little-known substances have a profound impact on all of our lives. Endocrine disruptors pervade modern manufacturing, food packaging, and food production (TEDX 2018). They are, in a word, ubiquitous.

The endocrine disruptor bisphenol A (BPA) is perhaps the most well-known and the most common endocrine disruptor. BPA is a plasticizer and resin. Without BPA, one-use plastic water bottles would not crush underfoot without cracking, thicker plastic used in Tupperware would not clearly show the delicious food inside, and canned tomatoes would consistently rust through their containers, leaving a bloody red mess. Many of us are more familiar with BPA as a loss, having come across the many products labeled "BPA Free" in the grocery store. Just those instances make BPA ubiquitous in our lives. But those examples barely scratch the surface. Each year in the US, we manufacture over two billion pounds of BPA. Worldwide, BPA production tops eight billion pounds, making it a multimillion dollar industry (EPA 2010; CDC 2016). It lines cans, wraps our food, sprays our produce, and colors our toys. Nearly every piece of processed food in America has been exposed to BPA, either through a nozzle, pipe, or package. Nearly every American, 93 percent, carries BPA in their body, detectable in blood or urine

(NIEHS n.d.; Biello 2009). And yet, in talking about my project with people, I encountered very few who knew what BPA was, what it does, or why it matters.

BPA is a weakly estrogenic chemical, meaning that it has been shown to interact with estrogen receptors acting as either an agonist or antagonist. BPA has been linked to female and male infertility, precocious puberty, breast and prostate cancer, and metabolic disorders like polycystic ovary syndrome (Jalal et al. 2018; Konieczna, Rutkowska, and Rachon 2015). Those are among the milder effects. Powerful estrogens, like diethylstilbestrol, which at one point was in most beef and chicken produced in the US, have been linked to aggressive and rare cancers, significant reproductive abnormalities, and fertility problems.

Why, if these substances have been linked to such effects, do most people not know about them? What does the US do about such substances? Why do we still use these chemicals? When I first learned of endocrine disruptors in my last undergraduate year, I considered all of those questions and pursued a doctorate to find answers. This dissertation is the result.

This Dissertation

My focus in this dissertation is on the endocrine disruptor concept and the associated category of toxic substances called endocrine disruptors. Throughout, I examine the concept and substances from a scientific, political, and social perspective, especially during the period from 1991 to 1996. I am interested in how endocrine disruptors came to be scientifically, politically, and socially interesting.

Researchers first defined the concept and the category in 1991. At a work session organized by environmental health scientist Theo Colborn, twenty-one handpicked researchers determined that chemicals contaminating natural environments posed a risk to the wildlife in those environments (Colborn and Clement 1992; Abboud 2014). The group analyzed studies showing negative reproductive and developmental effects as a result of chemical exposure before agreeing to two claims, laid out in what is called the Wingspread consensus statement. Those two claims make up the endocrine disruptor concept that is the focus of this dissertation. The concept is as follows:

1. That chemicals that interfere with the hormone system of organisms to negative effect exist and are rightly called endocrine disruptors, and
2. That endocrine disruptors pose a clear and immediate threat to the health of wildlife and human populations.

In conjunction with that concept, Colborn and her colleagues proposed endocrine disruptors as a category of toxic substances in 1991. The category is made up of those chemicals to which the concept applies, the chemicals that threaten the health of humans and wildlife through their endocrine activity. The group laid out four characteristics of endocrine disrupting chemicals:

1. The chemicals affect different developmental stages differently. Effects seen in embryos, fetuses, or perinatal organisms differ from those seen in adult organisms.
2. The chemicals often affect the offspring of individuals exposed.
3. At what point an organism is exposed to the chemical changes the effects of that chemical.

4. When exposure occurs during development, effects may not be seen until adulthood. (Colborn and Clement 1992)

This dissertation traces the trajectory of the concept and the category from 1991 forward. In particular, I focus on two threads. First: how the scientific, social, and regulatory nature of the concept effected its interaction with actors in various areas. And second: how the lack of substance in the proposed category was received and how it did or did not cause problems in scientific, social, and regulatory settings.

When the researchers at Wingspread proposed the endocrine disruptor concept, they clearly and explicitly situated it as a scientific, social, and regulatory object (Colborn and Clement 1992; Colborn, vom Saal, and Soto 1993). In their statement, the researchers lay out their goals moving forward on the problem of endocrine disruptors, and those goals included furthering scientific study, increasing public awareness of the threat, and achieving regulatory action. They make clear that they do not see scientific investigation as sufficient for addressing the problem posed by endocrine disruptors, arguing that social and regulatory action are necessary. An examination of their actions after Wingspread shows that proponents of the concept pursued each of those goals, further cementing the endocrine disruptor concept as a tripartite concept, scientific, social, and regulatory.

As I explore in this dissertation, the multi-faceted nature of the concept caused scientific, social, and regulatory actors to interact with the concept and each other in interesting ways. Never could the scientific research conducted on endocrine disrupting chemicals be separated from the question of whether and how the chemicals should be regulated. Nor could the pressure to address the public fear of endocrine disruptors not

influence the scientific and regulatory decisions of the time. In each chapter of this dissertation, I focus on how the three parts of the concept impacted its trajectory from original inception in 1991 to regulation in 1996 to discussions in 2018.

Throughout my work, I also follow on a second thread, the emptiness of the endocrine disruptor category. In the Wingspread consensus statement, Colborn and her colleagues laid out the characteristics of endocrine disrupting chemicals. In essence, they proposed a box. The box's edges were made up of the known characteristics of endocrine disruptors from the Wingspread meeting. That box proposed in 1991 then had to be filled, raising a question of what chemicals fit in the box.

My project tells the story of how that box was created, put out into the world, and acted upon, even as the question of its contents remained. That box, though quickly filled with chemicals by proponents of the endocrine disruptor concept, is contentious into the modern day, with little agreement on what counts as an endocrine disruptor. Throughout this dissertation, I pay attention to the many different actors and kinds of actors who interacted with the box (endocrine disruptors)—how they understood what endocrine disruptors were, what scientific evidence said of endocrine disruptors, and whether and how endocrine disruptors should be regulated.

The bulk of my analysis ends in 1996, when Congressional action in the US codified the concept and the category in the context of serious scientific disagreement. In 1996, Congress passed the Food Quality Protection Act and amendments to the Safe Drinking Water Act. Both acts amended the Federal Food, Drug, and Cosmetics Act and Federal Insecticide, Fungicide, and Rodenticide Act, which charged the EPA with the regulation of pesticide levels in food and water. The Food Quality Protection Act and the

Safe Drinking Water Act required the EPA to screen chemicals for possible estrogenic activity. Neither act silenced arguments over the characteristics of endocrine disruptors nor questions over the threat they pose to humans and wildlife. In 2018, those arguments and questions remain, playing out in new and old arenas. What Congressional action did do for the endocrine disruptor concept and category was cement their place as continuing areas of research and discussion. With federal laws requiring action on the substances, regardless of widespread dissent, endocrine disruptors remain relevant.

In response to the Food Quality Protection Act and the amendments to the Safe Drinking Water Act, the EPA convened the Endocrine Disruptor Screening and Testing Advisory Committee to determine the best methods to evaluate hormonally active pesticides. In 1998, the Committee released its final report, urging the EPA to expand the testing of pesticides to commercial chemicals, environmental contaminants, cosmetics, polymers, and several other substances, as well as to include estrogen, androgen, and thyroid effects (EDSTAC 1998). Following the Committee's report, the EPA spent close to a decade creating the initial list of chemicals to be tested and the tests that would be used to screen those chemicals.

The result of the Committee report and subsequent discussions is called the Endocrine Disruptor Screening Program. The EPA established a two-tiered screening program for possible endocrine disruptors. The purpose of Tier 1 is to identify the chemical substance's interactions with estrogen, androgen, and thyroid screening pathways (Marty 2014, 1). Tier 2 aims to identify the adverse effects from the substance's interactions with the endocrine pathways identified in Tier 1 as well as to generate dose response data. The Endocrine Disruptor Screening Program represents the

totality of the US's attempts to regulate possible endocrine disruptors. Once a chemical has successfully made it through the program, companies are able to use the chemical largely with impunity. However, the program has received much scrutiny (Marty and O'Connor 2014; Maffini, Neltner, and Vogel 2017).

The story I tell here largely takes place between the initial conceptualization of the endocrine disruptor concept by Colborn and her colleagues in 1991 and the modern debates over the efficacy of the Endocrine Disruptor Screening Program and the threat posed by endocrine disruptors. My dissertation sits at a meeting point between studies of history of science and science policy. I use historical methods to comment on past and current science policy issues surrounding the endocrine disruptor concept and category. As such, key to my work but not central to this publication are the ways in which the endocrine disruptor story fits in to the larger history of toxic substances regulation in the US, a history that continues in 2018.

Surrounding endocrine disruptors and their regulation in the 1990s is a path-dependent story about how commitments made in the 1970s drove what happened to endocrine disruptors in the 1990s. Endocrine disruptors, at their root, are environmental contaminants and our concern about them and regulation of them can be traced to the environmental movement started by Rachel Carson's publication of *Silent Spring* in 1962 (Carson 1962a). In that work, Carson pointed to the direct impact of industrial and agricultural chemicals on the natural environments throughout the country and on human health.

Silent Spring and the work of early environmentalists like Carson accomplished several things integral to the story of endocrine disruptors: they raised public

consciousness about environmental issues, they demanded and saw the creation of an agency devoted to environmental threats (the Environmental Protection Agency or EPA), and they defined environmental concerns as political issues that citizens could demand action on. Carson and the environmental movement drove much of the discussion around endocrine disruptors, something that I intend to focus more on in later work. For this dissertation, I keep endocrine disruptors as the focus, as impactful and important substances in and of themselves.

Several other historical trends played out in the endocrine disruptor story I tell here: the US regulatory system's focus on cancer endpoints to determine toxicity, the post-World War II boom in chemical development and use, the setup of the US regulatory system throughout the twentieth century. Each historical path created a set of constraints that the story of endocrine disruptors unfolded within during the 1990s. Without the commitments made and the systems set up in the preceding decades, the regulation of endocrine disruptors would have looked very different and there are many interesting stories to be told about how the bureaucratic structure created in the 1970s led to a very particular set of circumstances surrounding endocrine disruptors in the 1990s. I refer to all those historical trends in this work, but here I am telling a story about endocrine disruptors and how a small group of scientists took advantage of the system created by Carson and the environmental movement, by the US emphasis on cancer, by the reactionary nature of US regulations, to get a new category of chemicals noticed and regulated.

I focus on endocrine disruptors for several reasons. First and foremost, endocrine disruptors are ubiquitous substances that impact all of our lives and therefore

understanding their history matters. The history of endocrine disruptors and their regulation impacts how we understand the substances, how we think about their effects, and how we justify their regulation. Who put forward the category and pushed for regulation influenced the type of regulation passed, regulation that is still in place in 2018. The lack of scientific consensus that developed around the endocrine disruptor concept and category in the 1990s has direct consequences for how we study and regulate the chemicals in the twenty-first century. The reliance on few human studies to justify the threat posed by endocrine disruptors continues to play out in industry response to regulations. The story of endocrine disruptors is a story of the past that informs the present. By understanding their history, who had a voice and how evidence was used, we can better reflect on what to do about endocrine disruptors moving forward.

I also draw attention to some interesting characteristics of endocrine disruptors as scientific and policy problems. As a category, endocrine disruptors perturb many toxicological assumptions or norms. They follow non-linear dose response curves, they are active in very small doses, they show effects decades or generations after exposure, and evidence of their effects continues to be interpreted in opposite ways: as an indictment against them or commendation for them (Anway et al. 2005; Braun and Gray 2017; Conolly and Lutz 2004; Lanphear 2017; Schug et al. 2016; Vandenberg et al. 2009; Wang and Baskin 2008; Wolstenholme, Goldsby, and Rissman 2013). They are a complex category of interest to varied actors, not simply corn farmers or cattle ranchers, baby bottle producers or tomato can manufacturers, environmentally conscious consumers or health aware buyers, but all those groups. There are few industries endocrine disruptors do not touch, making them a tricky regulatory hurdle.

From a science policy standpoint, the case of endocrine disruptors is unique. Many science policy problems follow one model. Under that model, the issue is well known and there is broad scientific consensus but for a small number of skeptics who become magnified by the media in a way that undermines policy progress. Vaccines, genetically modified organisms (GMOs), climate change, the effects of tobacco use all follow that model. In the case of climate change, almost every scientist in the world agrees that the actions of humans have caused the climate to change and that that change comes with damaging consequences. Yet, the very small minority who disagree continue to have a loud voice in social and political discussions. As Bill Nye put it early in 2017, "[media outlets] are doing a disservice by having one climate change skeptic and not 97 or 98 scientists or engineers concerned about climate change" (Resnick 2017). Such presentation of science has stymied policy action in a variety of ways, leading many to foretell disaster.

Endocrine disruptors are different. First, very few members of the public know what endocrine disruptors are or what they do. While there may be slightly more awareness of specific endocrine disruptors like BPA, even those are not well known. Just that makes endocrine disruptors interesting: a hugely impactful and ubiquitous group of chemicals virtually unknown. But endocrine disruptors differ in another way. Where many other science policy issues have broad scientific consensus, endocrine disruptors do not. The scientific community that studies endocrine disruptors is evenly split between believing that the substances pose a large threat to human health and believing that they have been overhyped and pose little threat. Consensus cannot even be reached on a definition for endocrine disruptors. Where vaccines and GMOs are cases of public

controversy perpetuated by a scientific fringe, endocrine disruptors are a case of in house, within science controversy that has not been resolved in nearly thirty years.

And yet policy progress was made within a very short five-year period. Where many are still trying to get climate change, a well-documented and agreed-upon scientific phenomenon, even acknowledged as a policy problem, a small group of researchers managed to get the deeply contested category of endocrine disruptors not only acknowledged but quickly and aggressively acted upon. In that way, endocrine disruptors are a unique policy case, interesting in their many differences from the norm.

That does not mean that they cannot also be useful in science policy discussions, however. As I stated in my prospectus at the beginning of this project, endocrine disruptors draw in and complicate many parts of the regulatory process. Their study and regulation in the 1990s sat at the confluence of a large number of interested parties—science, industry, government, consumers, civil society—and each of those actors and the individuals making up those groups had different interests in endocrine disruptors, different understandings of the scientific knowledge surrounding endocrine disruptors, and different concepts of who should act as expert in determining the use and regulation of endocrine disruptors. My historical analysis makes clear the conversations those parties had and therefore helps to illuminate one way a science policy problem comes in to existence and is addressed.

Through my examination of how different actors thought of endocrine disruptors and how they saw the science and regulation of endocrine disruptors fitting together, I have laid out the life trajectory of the chemicals in a way that helps to show how science policy gets done. My focus on the broad category means that I have ended up with a work

that is focused on a topic of relevance to any individual who shops at a grocery store. In that way, my project is a story of the past that informs that present. Endocrine disruptors are important, in and of themselves. The category encompasses chemicals that pervade every aspect of modern life and their regulation matters to everyone. It matters why new mothers stop to make sure they buy BPA free bottles in the grocery store. It matters why people think that chemicals in the water make people gay. It matters why Whole Foods hands out yellow receipts instead of white.[1] How did it come to be that such thoughts and actions were reasonable to people? How did they become justified? Those are some of the questions I am answering within this dissertation.

The Contents

I have divided this dissertation into five chapters, each with a different focus but drawn together by my examination of the effects of the tripartite nature of the endocrine disruptor concept and the lacking definition of the endocrine disruptor category. As a reminder, the concept proposed in 1991 encompassed two claims: That endocrine disruptors exist as a category of toxic substances capable of disrupting normal hormone function to negative effect; and that those chemicals pose a threat to the health of humans and wildlife. Proponents of the concept explicitly set it up as a scientific, social, and

[1] Thermal paper receipts, like those received as gas stations, grocery stores, and retail outlets, contain high levels of BPA. The BPA on the receipts is not chemically bound and therefore easily rubs off when handled, where it is then absorbed in to the skin. Studies have shown that sales associates who handle thermal paper receipts for eight hours per day have five times the amount of BPA in their body as the average American. For that reason, some stores like Whole Foods have begun to use thermal register tape that is BPA free. It is often yellowed as a result.

regulatory object, connecting it to a poorly defined category of substances. In each chapter of this dissertation, I trace different aspects of the scientific, social, and regulatory nature of the concept and the lack of substance in the category.

The title of this dissertation is *A Biography of Endocrine Disruptors*. My first chapter takes the biography concept quite literally. In Chapter 2, "Origin of the Endocrine Disruptor Concept," I lay out the historical roots of the endocrine disruptor concept. Though the start, end, or process could not have been known at the beginning of the life of the concept, understanding the genesis of the category requires an examination of previous forms, just like in embryogenesis. Precursors in embryogenesis do not look anything like the final organism on the surface, but they change and shape the final organism in key ways. Similarly, important precursors fundamentally changed the conversation surrounding hormonally active chemicals in ways necessary for the endocrine disruptor concept.

In order for proponents of the concept to reasonably situate the concept as scientific, social, and regulatory in 1991, previous scientific, social, and regulatory moments had to create a world in which that was reasonable. Necessary scientific discoveries, like the estrogenicity of non-estrogen resembling chemicals, and social and regulatory changes, like the awareness of the sensitivity of *in utero* development, helped to create the world where the endocrine disruptor concept and category could be taken seriously. In Chapter 2, using a developmental metaphor, I link together historical moments that came together to start the life of endocrine disruptors.

In my next chapter, Chapter 3 "The Life of Endocrine Disruptors (1991–)," I detail the trajectory of the concept and category in the years after their proposal in 1991.

In that trajectory, I take as my focus how proponents pushed the concept and category into different arenas and how actors in their arenas pushed back in a variety of ways. I argue that when proponents introduced the concept and category in 1991, they did not define key aspects of endocrine disruptors necessary for their study and regulation, things like mechanisms of action, and they also lacked key evidence necessary to support the idea that endocrine disruptor threatened human health. Throughout the history of endocrine disruptors, actors in different areas responded differently to those deficiencies, with scientific actors probing deeply at what was missing, social actors largely ignoring any missing pieces in favor fear-mongering, and regulatory actors filling in with politically useful pieces. Chapter 3 traces those actions and their effects into the modern day.

Following my history of the endocrine disruptor concept and category in the first chapters, I use my last three chapters to focus in on particular actors and their interactions with both. In Chapter 4, "Disagreement Dissected, The Spectrum of Agreement about the Endocrine Disruptor Concept in the 1990s," I categorize the varying scientific views on the endocrine disruptor concept as laying along a spectrum. On one side were those researchers who originally drafted the idea, who viewed the existence of and threat posed by endocrine disruptors as a proven fact. On the other side, different researchers argued that very little evidence supported what they called the endocrine disruptor hypothesis.

What I focus on in my chapter is the middle of the spectrum, where the majority of endocrine disruptor researchers fell. Many researchers in the 1990s viewed what they called the endocrine disruptor hypothesis as still needing more evidence to establish its validity. Those researchers were the ones conducting experiments on the substances and

contributing to our scientific understanding of their effects. And yet their voices are largely erased from the historical and scientific narrative of endocrine disruptors, leaving the debate over endocrine disruptors feeling polarized. Throughout Chapter 4, I highlight how the scientific aspects of the concept could not be separated from the social and regulatory aspects, leaving scientists weighing in on not only the evidence supporting the concept but also what should be done about endocrine disruptors. A full examination of the different views on the endocrine disruptor concept illustrates the scientific tensions at play in the 1990s, tensions that spilled over into the regulatory actions taken then as well as the discussion of endocrine disruptors in 2018, which remains polarized.

In my final two chapters, I examine the movement of the endocrine disruptor concept both into and out of the scientific sphere. Science does not occur in a box, separated from the rest of society where it remains untouched and unchanged except by scientific thought. That is especially true in the case of the endocrine disruptor concept, which was positioned clearly as social and regulatory as well as scientific. Chapters 5 and 6 examine how the different actors interacting with the concept impacted the actions of other interacting actors.

In Chapter 5, "How Non-Scientific Actors Affected the Scientific Discussion of Endocrine Disruptors," I focus on the ways in which endocrine disruptor science—scientific endeavors, scientific findings, scientific funding, scientists—was changed by a number of societal occurrences. The science of endocrine disruptors is a case where a scientific field was especially changed by societal actors like media, industry, and government. In the chapter, I demonstrate that societal actors can have an outsize role on scientific discussion. In the case of endocrine disruptors, actors like media and

government took a science that was fringe, pushed it to mainstream, and then contributed to the fragmentation of the scientific community interested in endocrine disruptors. That resulted in a field of study in which researchers largely cannot agree, something that has consequences for the regulation of a category of potentially harmful substances in 2018.

In my final chapter prior to the conclusion, Chapter 6, "How the Science of Endocrine Disruptors Made its Way into Regulation," I look at how a social opportunity and a carefully crafted scientific story led to regulatory success. In the chapter, I advance a two-part argument to explain how endocrine disruptors came to be regulated in the US. The first part deals with the social and regulatory landscape in the early 1990s that significantly aided proponents of regulating endocrine disruptors by creating a window of opportunity. The second part focuses on the work of endocrine disruptor researchers in Congressional hearings, where they used very specific scientific evidence to argue for a particular kind of regulation. As I demonstrate, the result of both the window of opportunity and the inclusion of very specific science was the Endocrine Disruptor Screening Program, the only regulation of endocrine disruptors in the US as of 2018.

I finish this dissertation with a conclusion oriented around the ways in which the history of endocrine disruptors plays out in the modern world. In 2018, the EU is still searching for a way to successfully regulate the chemicals (European Commission 2018b; Paun 2018). The US is struggling to update their regulatory testing requirements in an administration that has cut their budget significantly (EPA 2011a; EPA 2011b; Erickson, Hogue, and Morrison 2017; Song 2017). And the scientific community around the world continues to squabble over whether anyone should even be talking about endocrine disruptors (Zoeller et al. 2014; Nohynek et al. 2013; Vandenberg et al. 2009). Such things

make it clear that endocrine disruptors represent a contested but important category of chemicals. My dissertation makes clear that many of the most contested aspects of endocrine disruptors originated decades ago and were left unaddressed for reasons as trivial as personality of people. By considering current events and the historical ones laid out here, we end with a starting point for evaluating how we might move forward better.

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CHAPTER 2

ORIGIN OF THE ENDOCRINE DISRUPTOR CONCEPT

INTRODUCTION

In 1991, Theo Colborn and a group of twenty colleagues put forth the endocrine disruptor concept. They argued that many industrial and agricultural chemicals acted hormonally in the body, interfering with the normal action of hormones and resulting in negative health outcomes. Those chemicals, they claimed, affected both humans and wildlife, developing organisms and adult. And not just affected, but threatened the health and existence of. When Colborn and her colleagues introduced the concept, they situated it as a scientific, social, and regulatory object. Something that should be taken seriously in all three contexts.

This dissertation takes as its focus the endocrine disruptor concept and its tripartite existence. The subsequent chapters all pertain to different effects of the scientific, social, and regulatory nature of the concept after 1991. This chapter, however, starts before 1991 and the introduction of the concept in order to examine the scientific, social, and regulatory changes and discoveries necessary for the legitimacy of the endocrine disruptor concept in 1991.

When proponents introduced the concept in 1991, they relied on a body of scientific literature as well as specific social and regulatory systems in the US. For the endocrine disruptor concept to be taken seriously by scientists, policymakers, and larger US society, as proponents intended, proponents built on scientific knowledge, bureaucratic systems, and social concerns developed prior to 1991. For example, because

the concept largely focuses on environmental contaminants, earlier work by Rachel Carson and the environmental movement to establish the Environmental Protection Agency (EPA) was important in creating a regulatory system endocrine disruptors fit in as well as a social consciousness that environmental concerns were serious and important considerations.

In this chapter, I lay out seven necessary historical moments that contributed to the endocrine disruptor concept in 1991, along with other broader social and political changes that also contributed. I go through those seven steps using the metaphor of biological development. Using the metaphor, I link together preceding events into a cohesive narrative. Just as during the development of an organism, the development of the endocrine disruptor concept followed a series of steps each building on the next to allow for change and growth over time. Certain aspects of the modern endocrine disruptor concept depended on historical happenings that changed the conversation around hormonally active chemicals.

As I have constructed the narrative, the development of the endocrine disruptor concept has seven points, or punctuations, that I connect to seven aspects of human development: the release of an egg, fertilization, implantation, gastrulation, the transition from embryo to fetus, and fetal movement. Those seven stages connect to the following seven points necessary for the endocrine disruptor concept:

1. Release of an egg: That naturally occurring hormones can cause negative effects in humans; first established by the estrogen cancer hypothesis in the 1930s and expanded on by Roy Hertz in 1957,
2. Fertilization: That humans may be exposed to hormonally active substances via a

number of routes, including consumption of animal products and produce treated with such products; proposed by Hertz in 1957 as a steroid cycle,

3. Implantation: That unintentional exposure to hormonally active chemicals can have detrimental effects on human populations; made clear with the effects of *in utero* exposure to diethylstilbestrol (DES) in the 1970s,
4. Gastrulation: That chemicals need not chemically match estrogen or other hormones to act estrogenically in the body; established by researchers at the National Institute for Environmental Health Sciences (NIEHS) in the mid-1970s after problems with kepone production in Hopewell, Virginia,
5. Transition from embryo to fetus: That non-estrogen resembling industrial and agricultural chemicals can cause cancerous effects in humans; formally laid out at the first *Estrogens in the Environment* meet in 1979, where the term "environmental estrogens" was coined,
6. Continued transition from embryo to fetus: That non-estrogen resembling industrial and agricultural chemicals can cause noncancerous effects in humans; formally laid out at the second *Estrogens in the Environment* meet in 1985,
7. Fetal movement: That hormonally active industrial and agricultural chemicals in the environment can cause negative cancerous and noncancerous effects in humans and wildlife populations; demonstrated in 1990 with the conclusion of research on the Great Lakes region.

Beginning in 1957, Hertz established that estrogen activity could lead to noncancerous negative effects in humans, in addition to the cancerous effects already known. A first step toward a concept that takes as one of its claims that hormonal action

can lead to negative health outcomes. Shortly after, Hertz proposed a means by which humans may be exposed to excess estrogen in their environment, solidifying the threat posed by the hormone and also laying the groundwork for a concept that requires human exposure to unintended endocrine active substances.

A decade later, amid the burgeoning environmental movement that legitimized concerns about the environment and growing awareness of the effects chemicals could have *in utero* via thalidomide, the synthetic estrogen DES demonstrated the severity with which unintended exposure to hormonally active substances could affect the health of humans. With that, DES became not only the posterchild for endocrine disruption used in the 1990s, but also cemented the idea that hormonally active chemicals threatened the health of humans, key to the endocrine disruptor concept.

In the mid 1970s, the discovery of the estrogenicity of kepone, a chemical bearing no resemblance to estrogen, furthered the development of the endocrine disruptor concept by expanding the number of chemicals to which it applied. That served to widen the impact and threat of the concept in the 1990s, as well as spurring research on the many industrial and agricultural chemicals that could be endocrine active, research that built a foundation for the concept.

That research led, in 1979, to the creation of a new category of substances, environmental estrogens. Those substances and the research on their effects drove toward the final concept presented in 1991, both in terms of evidence produced and researchers involved. With the work on environmental estrogens came an acknowledgment of the many negative effects that could be caused by industrial and agricultural chemicals acting hormonally, an acknowledgement vital to the endocrine disruptor concept.

The final developmental stage for the endocrine disruptor concept came in 1990, when Colborn completed her work in the Great Lakes region. Colborn and others found that industrial and agricultural pollution in the Great Lakes caused a wide variety of effects in wildlife and humans. In Colborn's Great Lakes research, all the aspects of the endocrine disruptor concept, built up along the six preceding developmental stages, came together in one case leading directly to the birth of the endocrine disruptor concept.

Each of the seven moments discussed above contributed significantly to the proposal of the endocrine disruptor concept in 1991. The twenty-one researchers who proposed the concept relied on the scientific discoveries of the previous decades to make a case that industrial and agricultural chemicals could impact human health. They used the social and regulatory capital around environmental concerns and *in utero* effects of chemicals to make the case that their concept should be taken seriously as a social and regulatory concern as well as a scientific one. The developmental steps of the endocrine disruptor concept were necessary in the sense that they served as a series of historical contingencies that allowed for the tripartite formulation of the concept in 1991. Those steps and their role are laid out here.

Family History: Hormones and Cancer

Before detailing the developmental steps that produced the endocrine disruptor concept, it is important first to provide some context regarding the study of hormones and their effects, to make clear what changed along the developmental path detailed in the next sections. I will detail two main historical threads that play a large role in the endocrine disruptor story: the growing field of endocrinology (the study of hormones and

their glands) and the estrogen cancer hypothesis. Later actors in the development of the endocrine disruptor concept pull heavily on both of those threads. They are necessary to the concept's development just as the events in an individual's family history are necessary to theirs. The field of endocrinology establishes the normal actions of the endocrine system and the endogenous hormones within. Only with a footing in what should be happening can an assessment of disruption be made, a key aspect of the endocrine disruptor concept.

The estrogen cancer hypothesis, proposed in the 1930s, stemmed from the growing field of endocrinology. In 1923, estrogen was one of the first hormones discovered and through efforts to identify its normal behavior, researchers discovered its ability to cause cancer. That discovery established that hormones and hormonal actions could result in negative health outcomes, something that the endocrine disruptor concept depends on, given that it deals with the negative outcomes caused by hormonally active chemicals. Both threads, the growing field of endocrinology and the estrogen cancer hypothesis, are essential pieces of the endocrine disruptor story but are too far removed to be considered a part of its development directly, therefore acting as family history: a distant ancestor and a not so distant relative.

The Ancestor Who Sailed Across the Sea: Endocrinology

The family history of the endocrine disruptor concept can reasonably be said to have started in 1905 with the work of Ernest Starling. The concept, which describes substances that interfere with hormones, relies on an understanding and acceptance of hormones. That understanding and acceptance started in 1905, when Starling coined the

term "hormone" to describe "chemical messengers … [that] have to be carried from the organ where they are produced to the organ which they affect by means of the blood stream and the continually recurring physiological needs of the organism must determine their repeated production and circulation through the body" (Starling 1905a, 339).[2]

With that statement, Starling described the process of chemical messaging used within the body as well as the messengers, hormones. Starling's definition of hormone, presented in his first Croonian lecture of 1905 to the Royal College of Physicians of London, came out of his work with his brother in law, William Bayliss, on secretin (Bayliss and Starling 1902; Henderson 2005). Secretin, a hormone (though the word was not used at the time) that stimulates the pancreas, became the second substance found in the body to stimulate some sort of action, adrenaline having been extracted by John Abel in 1897 (Abel 1898; Aronson 2000).

Though Starling defined hormones in that first 1905 lecture, he did not refer to the substances again until his fourth lecture, delivered nine days later (Starling 1905d). He used it no fewer than seventeen times in that lecture, and thus began a new field of research on the chemical signalers of the body. In that way, Starling's use of the term "hormone" in 1905 acted as a sort of great-great grandparent to the endocrine disruptor

[2] The idea of substances that move through the body controlling physiological responses did not originate with Starling. In 1855, Claude Bernard used the term "internal secretion" to describe glucose in the liver (Bernard 1855). Some believe that internal secretion was used well before 1855 (Henderson 2005). Nor did the term "hormone" itself originate with Starling, the term having been thought up at a dinner at Caius College, Cambridge. At the dinner, Starling and biologist William Hardy determined that they needed a word to describe stimulating substances in the bloodstream. Classicist W.T. Vesey suggested the Greek verb for excite (*ormao*) and the term appeared in Starling's 1905 lecture (Henderson 2005, 9).

concept, a distant ancestor that had to immigrate to a new land and lay down roots for the later life of endocrine disruptors to occur. Without an understanding of endocrinology—how hormones usually work—it would have been difficult to claim that anything was being disrupted later.

The study of hormones grew rapidly after 1905.[3] Edward Calvin Kendall purified thyroxine in 1914 (Kendall 1914; Kendall and Osterberg 1919). Frederick Banting and Charles Herberg Best characterized insulin in 1921 (Banting and Best 1922; Banting and Scott 1923). And in 1923, Edward Aldebert Doisy and Edgar Allen successfully isolated the follicular hormone from the grape-sized ovaries of hogs (Allen and Doisy 1923). The follicular hormone extracted by Doisy and Allen, and later crystallized independently by Doisy and Adolf Butenandt, was later renamed estrone, one of several natural estrogens—the premier sex hormone and the hormone most often mimicked or blocked by endocrine disruptors (Butenandt 1930).

The discovery of estrone started the intense study of one particular kind of hormone: estrogen. The knowledge produced about the functioning of estrogen in the body, particularly when given at certain developmental points or in high quantities, established how the hormone worked so that later researchers could identify when

[3] The rapid growth of endocrinology led to an increasing recognition of its importance, as demonstrated by the many Nobel Prizes awarded to early endocrinologists. Frederick Grant Banting and John James Rikard Macleod received the Nobel Prize in Physiology or Medicine in 1923 for their work on insulin (Nobel Media 2014a). Adolf Butenandt received the Nobel Prize in Chemistry in 1939 (Nobel Media 2014b). Edward Calvin Kendall, Tadeus Reichstein, and Philip S. Hench received the Nobel Prize in Physiology or Medicine in 1950 for their work on adrenal gland hormones (Nobel Media 2014c). Edgar Allen was nominated for the award four times, though he never received it (Nobel Media 2014d).

estrogenic activities went astray. The first identification of awry estrogen activities came with the estrogen cancer hypothesis. While the field of endocrinology continued to grow, with researchers producing more work on the actions of more hormones, the estrogen cancer hypothesis became a key part of the field and began research into the negative effects of hormones.

Closest Known Relative: The Estrogen Cancer Hypothesis

The discovery and isolation of estrone in the late 1920s was followed by concentrated study of the effects of estrogens in the body. From that study emerged the estrogen cancer hypothesis, which held that estrogen played a causative role in the development of cancer in estrogen-responsive tissues (Hertz 1977).

The first evidence for the hypothesis came in the late nineteenth century and early twentieth century when researchers showed that removing the ovaries of mice and humans stopped the progression of breast cancer (Loeb 1919; Beatson 1896). Given that the ovaries produce estrogen in the body, their removal and the subsequent amelioration of breast cancer implied a role for estrogen in the progression of cancer. That role was further solidified in 1937, when Allen and his colleagues showed that treatment of rat vaginas and uteri with estrogen resulted in uncontrolled cell growth generally associated with cancer (Allen, Smith, and Gardner 1937).

At the same time, in the late 1930s and early 1940s, several clinical preparations of estrogen became available for use in humans. The first was diethylstilbestrol (DES), an artificial estrogen developed in the labs of Edward Charles Dodds and Robert Robinson at the University of Oxford in 1938 (Dodds et al. 1938). DES was an orally-effective,

lightweight powder, approximately 150 times cheaper than natural estrogen extracts (Meyers 1983; Abboud 2015). When the Food and Drug Administration (FDA) first approved DES in the US in 1941, physicians prescribed the drug to millions of women for menopausal symptoms, postcoital contraception, and a variety of other hormonal issues (Meyers 1983). That number only increased when, in 1946, studies by Olive Watkins Smith and her husband George van Siclen Smith indicated that DES could be used to prevent miscarriages during pregnancy (Smith and Smith 1946; Smith 1948; Smith and Smith 1949). The FDA approved DES for that indication in 1947 (Langston 2010, 48). Between 1948 and 1971, somewhere between four and eight million pregnant women took large doses of DES, exposing both them and their fetuses to that artificial estrogen (McLachlan 2016).[4]

A year after the initial FDA approval of DES, in 1942, the US approved a second estrogen preparation, Premarin (Stefanick 2005). Premarin, manufactured by Wyeth, was a mix of conjugated equine estrogens extracted from the urine of pregnant mares and marketed as a treatment for menopausal symptoms (Stefanick 2005). Following the release of both estrogen-like medications, Premarin and DES, a slew of physicians made case reports linking the occurrence of breast and endometrial cancer in women with previous exposure to estrogen therapies (Hertz 1977; Allaben and Owen 1939; Auchincloss and Haagensen 1940; Parsons and McCall 1941; Fremont-Smith et al. 1946;

[4] Within endocrine disruptor literature, DES is almost always discussed with reference to its use in pregnant women. However, between 1941 and 1983, the agricultural industry in the US used DES as a growth hormone in livestock. By 1971, ranchers fed 75 percent of US beef livestock DES (Epstein 1990, 278). The effects of the daily exposure to DES residue left in meat are relatively unknown and rarely discussed within endocrine disruptor literature.

Østergaard 1954; Wallach and Henneman 1959). Though the reports were often on very small samples of selected populations of women, they added some weight to the estrogen cancer hypothesis.

Animal research throughout the 1950s added even more. By the middle of the twentieth century, researchers had demonstrated that added estrogen consistently resulted in tumors in five different species and eight different tissues. When administering estrogen to dogs, hamsters, mice, rabbits, or rats, researchers routinely found tumors in the bone marrow, breast, cervix, endometrium, kidney, ovary, pituitary, and testicle (Hertz 1977). Though that seems like clear and obvious support for the estrogen cancer hypothesis, researchers had failed to show that estrogen administration in primates resulted in cancerous growth, which left the application of animal findings to primates, and humans in particular, unclear (Hertz 1977). The applicability of animal studies to human populations plagued the estrogen cancer hypothesis in much the same way that it plagues the endocrine disruptor concept, as detailed later.

Regardless, the estrogen cancer hypothesis drew attention to a potential mal-effect from exposure to estrogen. Though only focused on cancerous effects, the linkage between hormones and negative health outcomes was necessary for the development of the endocrine disruptor concept. The linkage between estrogen and cancer opened the door for the study of other potential negative effects following exposure to hormones. That study began in 1957, which is where I begin the developmental story of the endocrine disruptor concept.

Conception: Non-Cancer Effects and Steroid Cycles

The purpose of using the developmental metaphor throughout the rest of this chapter is to link together necessary historical steps for the concept, historical steps that the endocrine disruptor concept depended on to make sense. From 1957 to 1991, several discoveries established new facts that form key aspects of the concept. The first two of those discoveries go hand in hand: noncancerous negative effects of estrogen and a method for humans to be exposed to exogenous estrogen. Concern over toxic chemicals revolves around two things, the effects of the chemicals and whether or not humans will be exposed to levels of the chemical sufficient to cause those effects. The estrogen cancer hypothesis began to establish the negative effects of excess estrogen exposure. In 1957, Roy Hertz added to that, allowing for an entirely new class of outcomes connected to such exposure. Later that same year, he also laid out how humans might be exposed to estrogen at high enough levels to cause such outcomes. Seen from a developmental perspective, the identification of noncancerous effects from excess estrogen exposure acts as the release of an egg, a large part of the developing threat of endocrine disruptors, but not enough on its own. Only when combined with a route of exposure, Hertz's steroid cycle, is the egg fertilized and combined with a second necessary part for further development.

Release of the Egg: Non-Cancer Effects of Estrogen

The estrogen cancer hypothesis provided a foundation for the endocrine disruptor concept, supported by some of the first research on the negative effects of hormones. The endocrine disruptor concept deals heavily with the negative health outcomes associated

with exposure to hormonally active chemicals. However, those negative health outcomes are primarily noncancerous. Throughout the twentieth century, the US regulatory system dealt almost exclusively with carcinogens, focusing on cancer endpoints to assess the toxicity of a chemical (U.S. Congress Senate 1991, Testimony of Eleanor Chelimsky). Endocrine disruptors have been linked to many cancers, but they have also been linked to many other health outcomes: decreased fertility, reproductive anatomy abnormalities, reproductive disorders (Schug et al. 2016). One of the main arguments made by proponents of regulating endocrine disruptors in the 1990s was that testing only for cancer endpoints would not adequately identify endocrine disrupting chemicals causing noncancerous problems (U.S. Congress House 1993; U.S. Congress House 1995). That is why the developmental story of the concept begins in July of 1957, when Roy Hertz identified noncancerous negative effects caused by exposure to exogenous estrogen.

In 1957, Hertz, the director of the endocrinology section of the National Institutes of Health's National Cancer Institute, published a report on four children accidentally exposed to large amounts of estrogen. In his report, Hertz notes that the children—three males and one female, ages five to ten—developed breasts and other symptoms generally not seen until the onset of female puberty (Hertz 1958). While investigating those symptoms, Hertz tested vitamins that each child took each morning, finding that each capsule contained the equivalent of 150μg of estrone. That estrogen exposure, according to Hertz, accounted for the symptoms in the children and marked the first-time exposure to hormones had been linked with a negative health outcome other than cancer (Hertz 1958).

Following his case presentation, Hertz identified exogenous estrogen as a concerning toxic chemical (Hertz 1958, 210). Throughout his article, Hertz acknowledges the increasing use of estrogenic compounds in pharmaceutical and agricultural practices, establishing his article as the first publication indicating adverse health effects other than cancer as a result of exposure to endocrine-active substances. That establishment can be likened to the release of an egg, a necessary first step for the later endocrine disruptor concept dealing with cancerous and noncancerous effects of hormonally active chemicals. However, for the effects of excess estrogen to be concerning, something that dictates funding allocation and researcher interest, they needed to be paired with a way for humans to be exposed to them. The egg needed to be fertilized, which it was later in 1957.

Fertilization: Roy Hertz's Steroid Cycle Idea

Following his identification of noncancerous effects of hormone exposure, Hertz laid out how humans might be exposed to such hormones. At the end of 1957, he talked about a "steroid cycle" in his discussion of an article on the effects of hormones used in livestock (Gassner 1957, 211). He stated that

> …[W]e have to consider that the introduction of… [hormones into cattle feed lots] leads to the exposure…of individuals who might otherwise not ever in their lives come in contact with such materials… This is not a theoretical consideration because we…now have encountered two families, each with two children, presented with simultaneously developing gynecomastia attributable to the accidental contamination of vitamin capsules by estrogens during

> manufacture. If such estrogens can, by stray handling, get into such pharmaceutical preparations, can they not very readily get where they are not wanted on the farm? …
>
> There is one additional consideration in this regard… The fecal excretion of these materials…will be dropped on the soil and…over generations there will be constant replenishment of the soil surface with steroidal substances of this kind. This in turn has its effect potentially on surface water-supply contamination and also potentially on the vegetable content of steroids in crops raised on such soil… I think that we are now actually setting up a steroid cycle in our environment, and we have to give very serious consideration to its implications for our subsequent development and growth and possibly reproductive functions. (Gassner 1957, 210–1)

Hertz's steroid cycle begins with the hormones given to cattle and other livestock. During the 1950s and 1960s, the agricultural industry gave most cows in the US the estrogen DES as a growth hormone (Epstein 1990; Marcus 1994). According to Hertz, those animals would excrete that hormone, creating a soil laced with steroids, which could then contaminate both water supplies and crops grown in the soil. Humans, through consumption of livestock, water, or crops, could become exposed to excess estrogen resulting in negative health outcomes. The cycle Hertz proposed was a means by which most individuals in the US could be exposed to estrogen.

Hertz's observations that unintended exposure to estrogen could impact the development of humans were borne out in two subsequent studies (Beas et al. 1969; Weber et al. 1963). For the development of the endocrine disruptor concept, Hertz's work

on effects and exposure routes were pivotal. Hertz was one of the first to establish the extended risks of increased hormone use in US food production, outlining the negative effects the hormones could have in humans as well as a means by which they might be exposed. In that way, he opened the later possibility for endocrine disrupting chemicals, chemicals that act hormonally and so could lead to cancerous and noncancerous effects especially after they replaced many of the hormones used in food production in the 1950s. But Hertz and his work were largely localized, meaning that many researchers did not know about his revelations or pay them much attention. In order for the endocrine disruptor concept to gain the acceptance it did in the 1990s and in the modern day, something much larger needed to change, something Rachel Carson and her work *Silent Spring* precipitated.

Developmental Environment: Silent Spring and Thalidomide

This chapter and its developmental metaphor focus on specific moments in history that the endocrine disruptor concept depends on because they established certain necessary facts, shifted the focus in fields of research, or changed regulatory priorities. However, over the course of the thirty-year developmental process of the concept, more is going on than the historical moments highlighted as different developmental stages. When organisms develop, they move through different stages in a linear way, but pervading the entire process is their developmental environment, the conditions in which they are developing. Those conditions can include whether the pregnant woman drinks or smokes, the external temperature where an egg is laid, or the availability of certain nutrients in the environment. The conditions impact many different parts of the

developmental process, in innumerable and sometimes unknown ways.

Similarly, the changing world throughout the twentieth century impacted the development of the endocrine disruptor concept. In particular, two changes—the environmental movement and the effects of thalidomide—made room for the endocrine disruptor concept. The concept is made up of several concerns: the impact of chemicals on human health, on the environment, on a developing organism. For people to take the concept seriously, those same people also had to consider legitimate that chemicals could harm human beings, the environment, and developing organisms. The environmental movement legitimized concerns about the impact of humans on the environment and vice versa, while revelations about the *in-utero* impact of thalidomide legitimized concerns about the impact of chemicals on development. Both make up important pieces of the endocrine disruptor concept's developmental environment.

Silent Spring and the Environmental Movement

In the 1950s, when Hertz identified excess hormone use as a risk to the health of humans, few Americans were paying attention to environmental threats—either those posed by the environment or to it. Instead, America was focused on other matters. During the late 1950s, the US was fighting the unpopular Vietnam War, racing toward the moon, and experiencing a revolution in civil rights. Environmental concerns did not take center stage. However, the endocrine disruptor concept could thrive only in a world where individuals take environmental concerns seriously. The publication of *Silent Spring* and the beginning of the environmental movement partially created that world.

Endocrine disrupting chemicals are environmental toxins. The threat they pose is due to their effects in humans as part of the environment (in water, food, and other products) and their effects in wildlife in the environment. Researchers first identified the effects of such chemicals in wildlife species as part of research stemming from environmental concerns. For that reason, Rachel Carson and her publication of *Silent Spring* make up the developmental environment of the endocrine disruptor concept. The environmental movement, rather than acting as a particular catalyst for the concept as Hertz's work did, instead permeated all aspects of its development after the 1960s, driving research, public concern, and regulatory attention.

Silent Spring, published by Houghton Mifflin in September of 1962 after Carson wrote a group of serialized essays for the *New Yorker*, became an overnight sensation (Carson 1962a; Carson 1962b; Carson 1962c; Carson 1962d). In the book, Carson claims that humans in modern society are poisoning themselves and the environment with reckless use of industrial and agricultural chemicals. Exposure to those chemicals, according to Carson, is so damaging that all wildlife in a given area may perish, resulting in a silent spring where once there was an abundance of life. *Silent Spring* provided a locus of scientific and public debate over the potential damage caused by the use of pesticides in particular, but industrial and agricultural chemicals more broadly (Griswold 2012). Carson largely won in the court of public opinion, resulting in widespread support for the ban of dichlorodiphenyltrichloroethane (DDT) in 1972 and the beginning of the environmental movement in the US (EPA 2017; Griswold 2012).

Following the publication of *Silent Spring* and the start of the environmental movement, the federal government established two organizations to study and keep track

of the environment. The first was the National Institutes of Environmental Health Sciences (NIEHS), officially created in 1969, though growing from a department of the National Institutes of Health established in 1966 (NIEHS 2017a). Congress charged the NIEHS with determining how the environment impacted human health. The second organization was the EPA, established in 1970 to protect the environment and human health (Ruckelshaus 1970; Nixon 1970).

Carson and the environmental movement proved key to the development of the endocrine disruptor concept. Her work invited the wider public into a new consciousness about industrial chemicals. *Silent Spring* was widely read, widely reviewed, and widely discussed (Griswold 2012). All that discussion made mainstream environmental issues and concerns about what man-made chemicals were doing to natural environments and in turn to human health. The everyday citizen in the US became aware of such concerns and through the creation of federal agencies, holding of Congressional hearings, and meeting of committees, environmental concerns became political issues.

For the endocrine disruptor concept, the situation of the environment as a social and political concern had two effects. First, it led to a proliferation of funding and attention for research on industrial and agricultural chemicals and their effects. With the creation of the EPA and the NIEHS, federal funds were used to investigate a slew of pesticides, most notably DDT, a known endocrine disruptor in 2018 (NIEHS 2017b). That research led to many of the following developmental steps for the concept. The second effect was that it changed the perspective on threats to and from the environment, allowing for concerns about them to be taken seriously. In that way, the endocrine disruptor concept and its proponents in the 1990s could be taken seriously, necessary to

their success in getting endocrine disruptors regulated and studied.

Thalidomide and In Utero *Exposure*

Silent Spring and the environmental movement made up a large part of the endocrine disruptor concept's developmental environment, but a second factor also bears mention: thalidomide and its *in utero* effects. Just as the environmental movement elevated environmental concerns to be taken seriously, the discovery of the effects of thalidomide elevated concerns about *in utero* effects of chemicals. A primary aspect of the endocrine disruptor concept is that so many of the chemicals cause effects after *in utero* exposure, and therefore the concept requires an acceptance that chemicals can act *in utero*, resulting in negative outcomes after birth.

A German pharmaceutical company, Chemie-Grunenthal, released thalidomide as a sedative in Europe in 1957 (Vargesson 2015). Quickly after its release, physicians began prescribing the drug to pregnant women to combat nausea and morning sickness. Though effective as an antiemetic, physicians soon linked thalidomide to a number of side effects, including phocomelia (Vargesson 2015). Phocomelia is a congenital condition where an infant's hands and/or feet are attached close to their trunk due to the underdevelopment or absence of limbs. In 1961, two researchers independently sounded the alarm regarding the teratogenicity of thalidomide and the drug was banned soon after (McBride 1961; Lenz et al. 1962).

The FDA never approved thalidomide in the US. An FDA reviewer, Frances Kelsey, halted the approval process due to her concerns about the safety of the drug (Vargesson 2015). However, the story of thalidomide and its effects certainly reached the

country, where the work of Kelsey was widely lauded. The impacts of thalidomide on the US regulatory system have been widely analyzed and will not be detailed here.

In the endocrine disruptor story, thalidomide played an additional role by drawing attention to the perturbation of development by chemical exposure *in utero*. By the 1990s, the ability of chemicals to act *in utero* was well known. Women knew not to drink or take drugs while pregnant. When proponents of the endocrine disruptor concept proposed that industrial and agricultural chemicals could be impacting the health of fetuses, that was not a foreign idea in the US. That familiarity made it much easier to situate endocrine disruptors as objects of social concern, which in turn made it easier to get endocrine disruptors regulated. That familiarity stemmed from the story of thalidomide and the research that came after.

Both thalidomide and the environmental movement changed key aspects of the consciousness in the US, making a place for the concerns detailed in the endocrine disruptor concept. The funding and attention that followed also facilitated the next developmental step of the concept, implantation and the effects of diethylstilbestrol.

Implantation: Estrogen Effects in Humans

By 1970, several discoveries had established key facts necessary for the endocrine disruptor concept. Researchers had linked estrogen with the onset of cancer. In 1957, Hertz demonstrated that hormones could also cause noncancerous negative effects. He also proposed a mechanism through which humans may be exposed to exogenous hormones. However, a piece was missing: evidence of serious negative health outcomes in humans after exposure to hormonally active substances.

Up until 1970, researchers had connected exposure to hormonally active chemicals with relatively few harmful effects in humans. Hertz described the development of gynecomastia and early puberty in children exposed to excess estrogen in 1957, but he saw the effects in a small population and the effects themselves were minor. Therefore, the threat posed by exogenous estrogen was difficult to extrapolate to larger human populations. Additionally, the children Hertz treated ingested excess natural estrogen, estrogen extracted from animals and purified, rather than a hormonally active man-made chemical. The endocrine disruptor concept focuses largely on manmade chemicals, as by the 1990s natural hormones had been removed from many food production processes. The endocrine disruptor concept depends on an acceptance that hormonally active chemicals can seriously impact the health of humans. With no evidence in humans, proponents would have had a difficult time convincing audiences in the 1990s of the threat posed by endocrine disruptors. The effects of DES served as that evidence.

In 1970, researchers connected prenatal exposure to DES with serious health problems, like aggressive cancers and reproductive tract abnormalities. The connection of *in utero* exposure to DES and health outcomes in humans serves as the moment of implantation in the development of the endocrine disruptor concept. Implantation, during development, allows the growing conceptus to access needed nutrients via the bloodstream of the pregnant woman. DES and its effects provided an outflowing of resources necessary for the twenty years of research that would support the endocrine disruptor concept in 1991.

Diethylstilbestrol (DES) Daughters and Sons

In 1970, Arthur A. Herbst and Robert E. Scully, physicians at Vincent Memorial Hospital in Boston, published a case report linking the occurrence of clear cell adenocarcinoma of the vagina[5] in young, twenty-year-old women with *in utero* exposure to DES (Herbst and Scully 1970). DES was an artificial estrogen given to pregnant women throughout the 1950s and 1960s to prevent miscarriages (Smith and Smith 1946; Smith 1948; Smith and Smith 1949; Abboud 2015). Though a study in 1953 demonstrated DES to be ineffective in that capacity, physicians nonetheless prescribed DES to more than four million women prior to 1971 (Dieckmann et al. 1953; Giusti, Iwamoto, and Hatch 1995; Abboud 2015). Herbst and Scully's 1970 case report, along with several studies throughout 1971 solidifying the connection noted by Herbst and Scully, led the FDA to prohibit the use of DES during pregnancy later that year (Greenwald et al. 1971; Hill 1973; Henderson 1973; Giusti, Iwamoto, and Hatch 1995; FDA 1972). Soon after Herbst and Scully's 1970 publication on the effects of *in utero* exposure to DES, researchers began noting other trans-generational effects of DES exposure: reproductive tract lesions, structural defects in reproductive organs like vaginas and uteri, and fertility problems (Giusti, Iwamoto, and Hatch 1995; NCI 2011). Individuals afflicted by those conditions were called DES daughters and DES sons.

DES served two roles in the development of the endocrine disruptor concept. First, the effects of the synthetic estrogen showed that exposure to synthetic hormones could cause major problems in humans. With the discovery of the effects of *in utero*

[5] Prior to Herbst and Scully's study, clear cell adenocarcinoma had rarely, if ever, been seen in patients under the age of fifty (Herbst, Ulfelder, and Poskanzer 1971).

exposure to DES, researchers had a population of several million individuals as testament to the dangers of exposure to synthetic hormones, especially estrogen. That proved key for continued research on hormonally active chemicals. Following revelations about the effects of DES, more resources became available for the study of endocrine active chemicals (Krimsky 2000). The NIEHS and other institutions provided funding and grants, researchers took a new interest, and the public engaged with the story of DES and its effects throughout the 1970s. Those nutrients allowed for continued work on industrial and agricultural chemicals, which in turn built up a body of knowledge necessary to the endocrine disruptor concept in 1991. The implantation of the concept through the identification of DES effects in humans directly led to the next developmental stage of the concept, gastrulation and the discovery of non-estrogenic chemicals acting estrogenically.

The second role that DES played in the development of the concept became clear only in the 1990s, when researchers proposed the concept. In 1991, DES served as the proof of concept for the endocrine disruptor concept. In the endocrine disruptor concept, proponents argued that endocrine disruptors posed a serious threat to the health of humans. But by 1991, little evidence supported that claim. Laboratory studies focused on animal models like mice in their research while field studies focused on fish, reptiles, and birds. Proponents lacked epidemiological studies with data on the effects of hormonally active chemicals. Except for the case of DES, which contained all of the aspects of the endocrine disruptor concept: the substance acted *in utero*, the effects were not apparent until later in life, exposure could cause many different effects. DES was, in fact, the perfect example of the endocrine disruptor concept because it clearly demonstrated that

unknowing exposure to hormonally active chemicals could have large impacts on health. That meant in the 1990s, proponents of the concept used DES as one of the only examples of endocrine disruptors impacting human health (Colborn and Clement 1992). In that way, DES and its effects served as a major moment in the development of the endocrine disruptor concept, forming one of its main foundations.

Gastrulation: Chemicals that are Estrogenic but Not Estrogens

The attention on DES brought the endocrine disruptor concept necessary resources. Those resources—the money, the researchers, and the attention—allowed for the further study of hormonally active chemicals. The studies that resulted helped to develop the endocrine disruptor concept through the 1970s and 1980s, through a period of gastrulation. During gastrulation, the mass of implanted embryonic cells goes from being made up of one kind of cell to many. In the case of the endocrine disruptor concept, gastrulation occurred through the expansion of substances to which the endocrine disruptor concept could apply.

Up until the mid-1970s, researchers identified hormonally active chemicals as a restricted group. In order to be hormonally active, a chemical had to be either a natural hormone, extracted and purified for use as a hormonal agent, or a man-made chemical that structurally matched natural hormones. In the mid-twentieth century, researchers imagined hormones and hormone receptors in the body as keys and locks (Raloff 2014; Raloff 2017; Peyser and Hayden 1999). A hormone needed a specific structure to fit into a specific hormone receptor and activate a hormonal response. The research on hormonally active chemicals fit that model. Both the estrogen cancer hypothesis and the

noncancerous effects identified by Hertz dealt exclusively with extracted natural estrogens. And diethylstilbestrol, the new mainstay example of hormonally active chemicals, structurally matched estradiol and was intentionally manufactured as a synthetic estrogen (Dodds et al. 1938; McLachlan 2016). Researchers designed DES as a key to fit in the estrogen receptor lock.

If, in 1991, the category of hormonally active chemicals only included those chemicals that structurally matched natural hormones, the endocrine disruptor concept would have applied to a much smaller group of chemicals. If endocrine disruptors needed to chemically resemble natural hormones to have an effect in the body, then the concern they raised would have been lessened. A method to identify such substances would have been obvious. Instead, during the mid-1970s, the category of hormonally active chemicals rapidly expanded with the investigation of the effects of kepone in Hopewell, Virginia. Researchers demonstrated that kepone, a highly-chlorinated molecule that in no way resembled estrogen, could act estrogenically in the body (Vogel 2012, 85).

The discovery that a much larger group of chemicals could act estrogenically in the body established an important piece of the endocrine disruptor concept: that many industrial and agricultural chemicals could disrupt hormone processes in the body. Kepone was a non-key that turned the estrogen receptor lock and opened the potential that an unknown number of other chemicals could do the same. Like during gastrulation when the kinds of cells diversify, the estrogenic actions of kepone diversified the kinds of things the endocrine disruptor concept applied to, which made the concept a far more serious and complex concern in the 1990s.

Kepone in Hopewell, Virginia

In early 1974, Life Sciences Products, a subcontractor of Allied Chemicals, began manufacturing large amounts of kepone at their plant in Hopewell, Virginia. Kepone, or chlordecone, is an organochlorine compound used in the production of several pesticides including Mirex, a fire ant killer (Reich and Spong 1983; McLachlan 2016). Soon after production started, workers reported experiencing "the Kepone shakes," severe tremors that affected balance and coordination (Reich and Spong 1983, 232). Local doctors could find no explanation for the shakes until one physician, Yi-nan Chou, sent a blood sample to the Centers for Disease Control and Prevention (CDC) in July 1975 (Epstein 1978). The CDC concluded that the blood sample from one of the plant workers contained high levels of kepone (Epstein 1978). Within months, the EPA and National Institute for Occupational Safety and Health (NIOSH) had been notified and began investigating the toxicity of kepone. When researchers went to Hopewell, they found that plant workers experienced high rates of sterility, loss of libido, tremors, and memory loss (Vogel 2012, 85). The EPA halted kepone production in August 1975 (Reich and Spong 1983).

The negative effects experienced by plant workers exposed to kepone spurred investigation of the toxicity of the compound (Vogel 2012). In those investigations, researchers found that mammals exposed to kepone responded as though they had been exposed to estrogen, and in lab screening tests, kepone bound to estrogen receptors (Eroschenko and Palmiter 1980; McLachlan 2016; Vogel 2012). However, kepone did not chemically resemble estrogen, raising the question of how a chemical that was not structured like estrogen could mimic its effects (McLachlan 2016). Kepone was a highly-chlorinated compound meaning that it should not have fit into the estrogen receptor in the

body. Kepone was not the right shaped key, and yet it still unlocked estrogen responses in the body.

A review of literature at the time showed that several other industrial and agricultural chemicals, like DDT, also acted estrogenically while not bearing any chemical resemblance to natural estrogens (McLachlan 2016; Kupfer and Bulger 1976). By the end of the 1970s, researchers began to realize that the action of hormones and hormone receptors was more complicated than a lock and key mechanism. That realization only continued research on the endocrine activity of various industrial and agricultural chemicals, including lead, polychlorinated biphenyls (PCBs), and bisphenol A (BPA) (Vogel 2012; Sullivan and Barlow 1979). Those studies connected such chemicals with sperm count declines, high rates of miscarriage, and infertility and grew the body of evidence the endocrine disruptor concept relied on in 1991 (Vogel 2012; Sullivan and Barlow 1979).

The growing understanding that substances not resembling estrogen could act like estrogen in a natural system opened the door for endocrine disruptors by showing that substances that were not hormones and not intended to act like hormones could nonetheless act as hormones. If only substances with a chemical resemblance to natural hormones could behave like hormones in the body and therefore be considered endocrine disruptors, scientists in 1991 would have been faced with a significantly shorter list of potential endocrine disruptors and a testing mechanism would have been relatively apparent. Manufacturers would have only needed to know if the chemical structure of their products matched the chemical structure of endogenous hormones. After kepone, testing mechanisms would have to test every chemical to see if it had surprising or

unexpected hormonal effects. Kepone began a gastrulation process in the development of the concept, expanding the chemicals of concern and the research used to support the endocrine disruptor concept in the 1990s.

Transition from Embryo to Fetus: Environmental Estrogens

Following the revelations about kepone and estrogenicity, researchers investigated the toxicity of industrial and agricultural chemicals in force. For much of the twentieth century, toxicological investigation of chemicals focused on carcinogenicity, or the ability of a chemical to cause cancer (U.S. Senate 1991, Testimony of Eleanor Chelimksy). Most if not all tests used in toxicology focused on cancer endpoints (U.S. Senate 1991, Testimony of Eleanor Chelimksy). The Ames test, which tests for mutagenicity by measuring mutations in bacteria exposed to certain chemicals, was often used for regulatory approval (Ames et. al 1973; Ames, Lee, and Durston 1973; Clayson and Clegg 1991). The focus on cancer only began to shift in the 1980s, after revelations surfaced about kepone and other workplace hazards causing reproductive problems in exposed workers (Vogel 2012).

The beginning shift away from the cancer paradigm in toxicology led to two important moments in the development of the endocrine disruptor concept: the creation of a new category of toxic substances and the connection of those substances to noncancerous endpoints. In 1979, at a workshop hosted by the NIEHS, John McLachlan and others coined the term "environmental estrogens" to describe industrial and agricultural chemicals that acted estrogenically and could cause negative health effects (McLachlan 1979). The term brought together all of the pieces of the endocrine disruptor

concept up to this point, joining the cancerous effects of natural estrogens, the trans-generational effects of DES, and the activities of kepone under one umbrella term.

Environmental estrogens, as a category, closely resembled endocrine disruptors. The coinage of environmental estrogens marked a shift in the development of the endocrine disruptor concept. Prior to, the developmental moments of the concept established important pieces of knowledge that the concept relied on in the 1990s. Environmental estrogens continued that, leading directly to the endocrine disruptor concept. The researchers who studied them became the researchers who studied (and study) endocrine disruptors. The research that supported their existence became the research that supported the existence of endocrine disruptors. In that way, the beginning of research on environmental estrogens serves as the shift from embryo to fetus in the development of the endocrine disruptor concept. Though there is no well-defined biological moment that separates an embryo from a fetus, many identify the shift as the point at which the conceptus becomes recognizably human in the sense of having all the major organ systems in place. Environmental estrogens are recognizably endocrine disruptors in that same way.

The shift from embryo to fetus for the endocrine disruptor concept continued with a second important moment in the 1980s: the connection between environmental estrogens and noncancerous effects. In 1979, when the term was coined, researchers saw the threat of environmental estrogens in their ability to cause cancer, a remnant of the decades long cancer paradigm in toxicology. By 1985, when the NIEHS sponsored a second meeting on environmental estrogens, the threat of the substances expanded to include noncancerous effects more seriously, especially noncancerous developmental

effects in children (McLachlan 1985). That expansion shifted environmental estrogens to more closely resemble endocrine disruptors, which act as toxicants to cause cancerous and noncancerous effects, especially reproductive and developmental effects. By the end of the 1980s, the key aspects of the endocrine disruptor concept had become clear: industrial and agricultural chemicals could act hormonally to cause reproductive and developmental problems as well as causing cancer.

Estrogens in the Environment I, 1979

In 1979, the NIEHS sponsored the first *Estrogens in the Environment* meeting in Raleigh, North Carolina, at the Velvet Cloak Inn. John McLachlan, then in the Laboratory of Reproductive and Developmental Toxicology at the NIEHS, organized the meeting around the goal of determining "what an estrogen is and how it works, and what effect estrogenic substances might have on human health" (McLachlan 1979, xv). In his write up of the meeting, McLachlan points to the estrogenic activities of substances like kepone to indicate the timeliness of the meeting (McLachlan 1979, xv).

At the meeting itself, attended by a multidisciplinary group of researchers including Frederick vom Saal and Ana M. Soto, both early proponents of the endocrine disruptor concept, researchers presented on mechanisms of action and potential environmental impacts of estrogenic chemicals. As reflective of the still recent emphasis on cancer endpoints, researchers at the meeting focused on cancerous effects of estrogens. At the meeting, researchers debated how estrogenic chemicals might be causing cancer. Prior to the 1970s, many researchers agreed that carcinogens caused cancer by inducing mutation in the affected organism (Clayson and Clegg 1991; U.S.

Senate 1991, Testimony of Eleanor Chelimsky). Therefore, to determine if a chemical was carcinogenic, researchers used mutagenic tests to determine if it was mutagenic (Clayson and Clegg 1991; U.S. Senate 1991). However, throughout the 1970s, some studies showed that traditional carcinogenic tests did not detect all cancer-causing agents (Clayson and Clegg 1991; U.S. Senate 1991, Testimony of Eleanor Chelimsky). DES, for example, when tested using the Ames test, did not test positively for genotoxicity (McLachlan, Newbold, and Bullock 1980). That left the researchers at the *Estrogens in the Environment* meeting, as well as researchers more broadly, considering by what other mechanisms a substance might cause cancer.

The *Estrogens in the Environment* meeting in 1979 is notable as being the location for the coinage of environmental estrogens to describe estrogenic chemicals that humans and other organisms may be exposed to with carcinogenic effect. The term identified a group of estrogenic chemicals, used in industry and agriculture, as potentially harmful to humans. Environmental estrogens and the research on their effects directly led to the endocrine disruptor concept, with the same researchers and same evidence involved in both. As research on environmental estrogens continued throughout the 1980s, the development of the endocrine disruptor concept progressed apace. However, a final aspect of the endocrine disruptor concept was still missing: the connection of environmental estrogens to noncancerous effects.

Estrogens in the Environment II, 1985

In 1985, McLachlan organized the second *Estrogens in the Environment* meeting, once again sponsored by the NIEHS (McLachlan 1985; McLachlan 2016). The second

meeting was precipitated by a report of widespread precocious puberty in children in Puerto Rico, where it had been shown that meat contained elevated estradiol levels (de Rodriguez, Bongiovanni, and de Borrego 1985; McLachlan 1985). According to McLachlan, that report shifted the focus to "the influence of estrogenic compounds on development in animals and humans" (McLachlan 1985, xix).

Within the foreword of the compiled works from the conference, McLachlan details the characteristics of environmental estrogens and the threat they pose. He argues that any chemical with estrogenic properties could cause cancerous and noncancerous effects in humans exposed to them through their environment (McLachlan 1985, xix). With that, McLachlan laid out a concept that bears striking resemblance to the endocrine disruptor concept.

Research on environmental estrogens in the 1980s directly built up the body of evidence used to support the endocrine disruptor concept in the 1990s as well as helping the development of the concept via the stimulation of many of the researchers who helped to propose the concept in 1991. Those researchers included vom Saal and Soto, both attendees at *Estrogens in the Environment* meetings and strong experimentalists in the 1980s looking at the effects of environmental estrogens (McLachlan 1979; McLachlan 1985). Along with Colborn, vom Saal and Soto authored some of the original material on endocrine disruptors, showing how directly environmental estrogens played a role in the development of the endocrine disruptor concept, truly moving it from embryonic to more and more fetal (Colborn and Clement 1992; Colborn, vom Saal, and Soto 1993).

Fetal Movement: Great Lakes Toxicology Research

By 1990, the individual facts and pieces of knowledge necessary for the endocrine disruptor concept had been laid out. However, the concept experienced one final developmental step before its birth in 1991: fetal movement. Fetal movement, a time referred to traditionally as quickening, is the moment when the pregnant woman can feel the movement of the fetus. The endocrine disruptor concept is not a person and does not have a mother. The moment of fetal movement for the concept instead occurred when all the individual pieces necessary for its legitimacy came together in a single case study. That case study, in the Great Lakes region of Canada and the US, sparked the initial conception of the endocrine disruptor concept by Colborn, who went on to call together the meeting where the concept was laid out (Colborn 1998b).

Great Lakes, Great Legacy?

Beginning in the 1950s, several studies suggested reproductive problems in some species of the Great Lakes region—specifically in the declining numbers of bald eagles (Broley 1958). Some linked those reproductive effects to the increasing industrialization of the area surrounding the Great Lakes, and following the publication of *Silent Spring* in 1962, to the use of DDT. Between 1960 and 1980, several other findings indicated potential environmental toxins in the basin, including the 1968 finding that mink-fed Lake Michigan coho salmon produced very few viable offspring and the studies throughout the 1970s showing the reproductive struggle of fish-eating birds in the region (Beland et al. 1991). Such findings resulted in intense rehabilitative efforts by Canadian and American environmentalists.

In 1987, the Conservation Foundation and the Institute for Research on Public Policy funded a two-year research program to evaluate the effectiveness of the efforts and the status of the Great Lakes basin (Colborn et al. 1990). Colborn worked with several other researchers on the project. Three years later, in 1990, Colborn and her five colleagues published *Great Lakes, Great Legacy?* In the book, they detailed almost three decades of research on the effects of industrial and agricultural chemicals in the Great Lakes ecosystem.

In *Great Lakes, Great Legacy?*, the researchers lay out evidence showing the reproductive problems and population declines of many Great Lakes species and the birth defects, elevated hormone levels, and trans-generational effects found in those same species (Colborn et al. 1990). The authors speculate that the effects noted are a result of exposure to certain chemicals, like 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin) and polychlorinated biphenyls (PCBs). The authors are more restrained in their comments on the health effects in humans, noting that data collected on cancer incidence and reproductive outcomes was inconclusive because such data is rarely collected in humans (Colborn et al. 1990). However, they do caution that chemical exposure could be detrimental.

Colborn's work in the Great Lakes brought together all the aspects of the endocrine disruptor concept: that industrial and agricultural chemicals act hormonally, thereby causing negative health outcomes in humans and wildlife, making the chemicals a threat to both groups. The 1990 publication of Great Lakes research marks the last developmental moment for the endocrine disruptor concept. By 1990, all the pieces for the concept had been established and only needed to be drawn together for its birth.

Arguably, one individual began that process in the 1980s. Before her death, Colborn spoke candidly about how her work in the Great Lakes gave rise to her thoughts on endocrine disruptors (Colborn 1998b). It was through that work that Colborn became aware of the preceding decades of research and called together the group at Wingspread to seriously discuss the effects of industrial and agricultural chemicals on humans and wildlife. That meeting bore out the endocrine disruptor concept.

Birth: The Final Formulation of the Endocrine Disruptor Concept

In 1991, the term "endocrine disruptor" was used for the first time. At the meeting called together by Colborn, twenty-one researchers discussed the effects of industrial and agricultural chemicals on humans and wildlife.[6] The attendees dubbed those chemicals endocrine disruptors to indicate that the substances worked by interfering with hormonal processes. Therefore, endocrine disruptors refer to a category of substances, a kind of thing in the world. The category has been populated for the past thirty years.

But that category is entwined with, in fact inseparable from, the endocrine disruptor concept. The endocrine disruptor concept, as stated in 1991, was: There are hormonally active agents in the environment (referring to natural environments as well as components of the human environment like food supply) to which humans and wildlife are exposed; exposure to those agents results in disruption of endocrine pathways and

[6] The twenty-one attendees at the Wingspread meeting were: Howard A. Bern, Phyllis Blair, Sophie Brasseur, Theo Colborn, Gerald Cunha, William Davis, Klaus D. Dohler, John McLachlan, John Peterson Myers, Richard E. Peterson, P.J.H. Reijnders, Glen Fox, Michael Fry, Earl Gray, Richard Green, Melissa Hines, Timothy J. Kubiack, Ana Soto, Glen Van Der Kraak, Frederick vom Saal, and Pat Whitten (Colborn and Clement 1992).

negative health outcomes in humans and wildlife, especially when exposure occurs during development; thus, endocrine disruptors pose a clear and immediate threat to the health of humans and wildlife. The individual pieces of that concept were established in the preceding decades, as the rest of this chapter has demonstrated. But they were brought together and named in 1991. Hence, the 1991 meeting is the birth of endocrine disruptors, both the category and the concept.

At the birth of the concept, the proponents established endocrine disruptors as subjects of scientific, social, and regulatory concern. When laying out their thoughts on the substances, the researchers clearly indicated that the substances needed to be investigated scientifically, made known to different publics socially, and acted upon politically. Those three goals dictated much of the work of the original proponents of the endocrine disruptor concept through the 1990s, as detailed in Chapter 3.

First Endocrine Disruptor Meeting, 1991

Following the publication of the Great Lakes report, Colborn called together a meeting in Racine, Wisconsin, at the Wingspread Conference Center. The endocrine disruptor concept was born at the work session on "Chemically-Induced Alterations in Sexual Development: The Wildlife/Human Connection," held 26–28 July 1991, when the term "endocrine disruptor" was first used by the twenty-one interdisciplinary researchers gathered.

At the meeting, researchers with a specific perspective weighed in on the problems posed by hormonally active chemicals. Colborn organized the meeting with John Peterson Myers, Director of the W. Alton Jones Foundation. The Foundation, and

Myers himself, sponsored environmental causes in the US. In organizing the 1991 meeting, both Colborn and Myers sought out researchers from diverse backgrounds who would be inclined to have pro-environmentalist concerns about endocrine disruptors. While the meetings sponsored by the NIEHS throughout the 1980s were attended by a broader and more representative group of researchers, the Wingspread meeting was not. The endocrine disruptor concept was formally laid out in 1991 by a group of activist researchers who then spent much of the next decade promoting the concept to scientific, public, and political audiences.

They started that process in January of 1992, with the publication of the Wingspread consensus statement and the associated scientific data presented at the 1991 work session. The twenty-one researchers articulated three purposes for their meeting and their released statement:

1. to integrate and evaluate findings from the diverse research disciplines concerning the magnitude of the problem of endocrine disruptors in the environment;
2. to identify the conclusions that can be drawn with confidence from existing data;
3. and to establish a research agenda that would clarify uncertainties remaining in the field. (Colborn and Clement 1992, 1)

Those three purposes introduced the endocrine disruptor concept as a scientific construct, one deserving of more research to further clarify what kind of thing endocrine disruptors are. Each purpose dealt explicitly with the collection and analysis of data in order to motivate a better research agenda to collect more data and further analysis.

After identifying endocrine disruptors as a scientific problem, the authors laid out what they considered facts about the chemicals. They claimed that manmade chemicals

had been released into the environment and that wildlife populations had already been affected by those chemicals. Those chemicals could generally be said to differentially affect embryos, fetuses, and adults, and to cause problems in offspring rather than exposed parents. The authors of the statement also claimed that problematic health effects caused by exposure to endocrine disruptors changed as a result of the developmental point when exposure took place. The researchers in the consensus statement then further claimed that humans could be affected by those same chemicals using DES as the proof of concept.

Importantly, the researchers at Wingspread did not lay out how to identify an endocrine disruptor nor what counts as endocrine disruption. In that way, the authors of the Wingspread statement created an empty category. Though they laid out general characteristics of endocrine disruptors, they left out specifics necessary for scientific and regulatory investigation of the substances. The sense that the endocrine disruptor category was laid out enough to feel solid, but empty of evidence, caused problems throughout the life of the concept from 1991 until 2018. This idea is explored further in Chapter 3.

In their statement, the Wingspread attendees introduced other aspects of the endocrine disruptor concept, namely expanding the concept as a regulatory and social problem. Within their released statement, the researchers made a series of recommendations. The first recommendation offered dealt with the regulation of endocrine disruptors and the associated required testing. The researchers stated that "[t]esting of products for regulatory purposes should be broadened to include hormonal activity *in vivo*" (Colborn and Clement 1992, 4). That recommendation is distinctly not

an establishment of a scientific agenda, but rather a regulatory one. Throughout the statement, the authors made clear that they considered endocrine disruptors to be a present threat to humans and wildlife, in itself not a purely scientific claim given the social construction of risk. With the addition of recommendations regarding regulatory action that should be taken on the substances, the proponents of the concept established the chemicals as regulatory problems, rather than purely scientific ones.

With a second recommendation, the authors further identified endocrine disruptors as social concerns. The authors stated that:

> The scientific and public health communities' general lack of awareness concerning the presence of hormonally active environmental chemicals, functional teratogenicity, and the concept of transgenerational exposure must be addressed. Because functional deficits are not visible at birth and may not be fully manifested until adulthood, they are often missed by physician, parents, and regulatory community, and the causal agent in never identified. (Colborn and Clement 1992, 5)

The recommendation here is less obviously social. The authors identified scientific and public health communities as the primary focus, however, their concern was that the effects of endocrine disruptors were going unnoticed due to lacking awareness about the substances. As made clear by their inclusion of physicians, parents, and the regulatory community in the recommendation, the authors aimed to increase general awareness of endocrine disrupting effects through social education.

Additionally, the authors use of the term “endocrine disruptor” further demonstrates their goal to center the endocrine disruptor concept as a social concern. As

Sarah Vogel reports, the term was the brain child of the meeting cohost, Myers of the W. Alton Jones Foundation. Myers, in thinking about a paper on climate change, coined the term "climate disruption" to convey negative implications not captured by "climate change" or "global warming" (Vogel 2012, 106; OED 2017a; OED 2017b; Lester and Myers 1989). He applied that same logic to the term "endocrine disruptor," meaning to clearly indicate the severe impacts of such disruption with the use of the term and to inspire reaction in those exposed to the term. In particular, popular media responds well to evocative terms, often resulting in broad dissemination of ideas connected to them.

The authors goal to establish the endocrine disruptor concept as a social object, as well as a scientific and regulatory one, became clearer in the time after the Wingspread statement was released, during which proponents of the concept spent most of their time spreading the endocrine disruptor concept in widely accessible formats like newspaper interviews (Luoma 1992a; Luoma 1992b; Krimsky 2000).

The birth of the endocrine disruptor concept as a scientific, social, and regulatory concern dictated much of the concept's later life. With the Wingspread consensus statement, proponents of the concept established their goals for the next decade: to scientifically investigate endocrine disruptors as a category, to socially expand awareness of the dangers posed by endocrine disrupting chemicals, and to politically act to ensure that those dangers were adequately regulated.

The Wingspread statement also pulls on all of the developmental pieces of the endocrine disruptor concept discussed in this chapter. In it, the authors make clear that they are concerned about cancerous and noncancerous effects, that they are aware of the hormonal actions of industrial and agricultural chemicals, and that DES serves as proof

that endocrine disruptors can cause detrimental effects in human populations. Those claims undergird the concept, in many ways allowing it to be taken seriously at the 1991 meeting and after. The knowledge produced and the changes wrought in the preceding decades allowed the concept to be as it was, allowed proponents to reasonably claim that hormonally active chemicals that disrupt normal processes to negative effect exist and that they threaten the health of human and wildlife populations.

Conclusion

In this chapter, I have detailed the thirty-year period during which the endocrine disruptor concept grew and developed, becoming firmer with increasing scientific knowledge and also broader with the inclusion of more substances and effects. Through that process, I sought to detail the contours of the endocrine disruptor concept in 1991: the claims made, the evidence used, and the historical changes relied on by proponents of the concept.

The seven crucial developmental steps for the endocrine disruptor concept are as follows:

1. That naturally occurring hormones can cause negative effects in humans; first established by the estrogen cancer hypothesis in the 1930s and expanded on by Roy Hertz in 1957,
2. That humans may be exposed to hormonally active substances via a number of routes, including consumption of animal products and produce treated with such products; proposed by Hertz in 1957 as a steroid cycle,
3. That unintentional exposure to hormonally active chemicals can have detrimental

effects on human populations; made clear with the effects of *in utero* exposure to diethylstilbestrol in the 1970s,

4. That chemicals need not chemically match estrogen or other hormones in order to act estrogenically in the body; established by researchers at the NIEHS in the mid-1970s after problems with kepone production in Hopewell, Virginia,
5. That non-estrogen resembling industrial and agricultural chemicals can cause cancerous effects in humans; formally laid out at the first *Estrogens in the Environment* meet in 1979, where the term "environmental estrogens" was coined,
6. That non-estrogen resembling industrial and agricultural chemicals can cause noncancerous effects in humans; formally laid out at the second *Estrogens in the Environment* meet in 1985,
7. That hormonally active industrial and agricultural chemicals in the environment can cause negative cancerous and noncancerous effects in humans and wildlife populations; demonstrated in 1990 with the conclusion of research on the Great Lakes region.

Looking back, it makes sense to link those steps together as a developmental process not because one caused another, but because the endocrine disruptor concept was dependent on each step in important ways. By examining each step as part of a process, it becomes clear why the endocrine disruptor concept looked as it did in 1991. In particular, it becomes clear why proponents were able to successfully promote the concept as a scientific, social, and regulatory object. Previous scientific discoveries, regulatory changes, and social concerns created an environment in the US where environmental

concerns like endocrine disruptors could be treated as a serious and immediate problem. Proponents of the concept used that to their advantage in the 1990s to gain support for regulatory change, which occurred in 1996.

The next chapter details the different responses to the scientific, social, and regulatory nature of the endocrine disruptor concept on its journey to regulation from 1991 to 1996.

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CHAPTER 3

THE LIFE OF ENDOCRINE DISRUPTORS (1991–)

INTRODUCTION

In Chapter 2, I detailed the scientific discoveries and historical changes that allowed proponents to introduce the endocrine disruptor concept as a scientific, social, and regulatory object in 1991. Within that concept, the researchers stated that: 1. Endocrine disruptors exist as chemicals able to interfere with normal hormone action and cause negative health effects, and 2. That those chemicals threatened human and wildlife health. In the Wingspread consensus statement, attendees like Theo Colborn and Frederick vom Saal crafted the two-part concept so that it connected to a series of goals: to continue scientific research on endocrine disruptors, to increase public awareness of endocrine disruptors, and to get endocrine disruptors regulated in the US. In setting those as goals, the proponents of the endocrine disruptor concept had to describe the category of endocrine disrupting chemicals.

Therefore, in 1991, proponents proposed not only the endocrine disruptor concept, but also the endocrine disruptor category. The category proposed by Colborn and her colleagues in 1991 was meant to contain all hormonally-active chemicals that threatened the health of human and wildlife populations, as dictated by the endocrine disruptor concept. Those chemicals, proponents argued, should be regulated and their threat be made known to the public. The category had a general outline, provided by the four characteristics of endocrine disruptors proponents laid out:

1. The chemicals affect different developmental stages differently. Effects seen in embryos, fetuses, or perinatal organisms differ from those seen in adult organisms.
2. The chemicals often affect the offspring of individuals exposed.
3. At what point an organism is exposed to the chemical changes the effects of that chemical.
4. When exposure occurs during development, effects may not be seen until adulthood. (Colborn and Clement 1992)

Those parameters lack specifics. In laying out the endocrine disruptor category, Colborn and her colleagues used very broad strokes, only including four general properties of endocrine disrupting chemicals while leaving out any detail of what counted as an endocrine disruptor, how to identify an endocrine disruptor, and through what mechanisms an endocrine disruptor functioned. In that way, the category presented was a box, or perhaps more accurately, a balloon. The category had a recognizable shape, something to contain dangerous hormonally active chemicals, but it was empty of the specifics needed to make it solid: what chemicals fit in the category, how to identify such chemicals, and how those chemicals work.

In this chapter, I trace the trajectory of the endocrine disruptor concept and category as they came into contact with actors from different spheres, scientific, social, and regulatory. Much of the story is led by the actions of proponents through the 1990s as they carried out their goals to increase the scientific study of, social awareness of, and regulation of endocrine disruptors. It was through that process that other actors were

exposed to the concept and category, ultimately leading to the regulation of endocrine disruptors in 1996.

In walking through the history of the concept and category in the 1990s, I focus on two threads: how proponents pushed both constructs into scientific, social, and regulatory spheres, and how actors within those spheres pushed back in various ways. Those are parallel narratives that took place largely between 1991 and 1996, the focus years of this chapter, but also into the modern day, which I focus on in a section at the end of the chapter.

The first thread of this chapter, how proponents pushed the endocrine disruptor concept and category into different realms, delves into the actions of proponents as they tried to situate both constructs in different contexts. Proponents made it clear in 1991 that they saw the concept and category as relevant in scientific, social, and regulatory contexts, and they spent much of the 1990s working to make that reality by introducing endocrine disruptors in different arenas through mediums like popular newspaper articles and Congressional hearings. Importantly, through that work, proponents used similar tactics in different arenas, not changing their claims or supporting evidence for different audiences. Additionally, the researchers began with regulatory and social audiences, rather than scientific ones, which set endocrine disruptors on a unique science policy trajectory that ended in quick regulation in the face of deep scientific division.

In this chapter, I bring out how proponents did that by walking through their actions in each of the years between 1991 and 1996. In those years, I also draw attention to the scientific, social, and regulatory changes that aided proponents in their attempts to situate the concept and category in those areas. Much of proponents' success in garnering

social attention for endocrine disruptors and regulatory action on them came from shifts in the 1990s that derived from decades-long contingencies. Among those, the shift away from the cancer paradigm in the early 1990s made room for a group of chemicals that act through non-cancer endpoints. In following the thread about proponents' work to make room for endocrine disruptors in different spheres, I incorporate the historical contingencies that aided them in that process.

The second thread of this chapter follows the response scientific, social, and regulatory actors had to the work of proponents. In particular, I highlight how those actors did or did not probe at the endocrine disruptor concept and category. Both the concept and category had major issues in the 1990s. Proponents lacked strong human evidence for endocrine disrupting effects, calling into question their claim that endocrine disruptors made for a public health crisis, and the category they presented lacked sufficient detail in terms of what chemicals counted as endocrine disruptors and how those chemicals worked.

Throughout the 1990s, actors in different spheres responded to those missing pieces differently. Social actors embraced the concept and category fully, as fear-inducing constructs that sold newspapers. Scientific actors responded oppositely, probing deeply at the concept and category with many ultimately rejecting some parts of both. Regulatory actors embraced particular aspects of the concept and category, those that proponents worked to present to them as politically actionable and valuable. Each actor's response was again impacted by historical movements that came to fruition in the 1990s, like the shift away from the cancer paradigm and focus on developmental perturbations, and also on social trends and truths of the 1990s, like the widespread fear of breast cancer

and waning masculinity. I include both in my analysis of the trajectory the concept and category in the 1990s.

In following both of those threads, I lay out the notable science policy path endocrine disruptors followed and the actions proponents took to make such a path possible. Those actions, and the resulting path, had consequences for the study and regulation of ubiquitous chemicals that impact all of our lives both in the 1990s and the modern day.

1991: Regulatory Introduction and the Cancer Paradigm

Just months after the Wingspread meeting where Colborn and her colleagues laid out the endocrine disruptor concept and category, proponents had an opportunity to begin on their project of getting endocrine disruptors regulated. Colborn introduced the concept and category in a regulatory setting for the first time in 1991 at a Senate hearing (U.S. Congress Senate 1991, Testimony of Theo Colborn). There, Colborn argued strongly for the need to regulate endocrine disruptors, using studies showing the effects of chemicals on pregnant women and children to make her point. The Senate hearing was the first attempt by proponents to push the endocrine disruptor concept and category into the regulatory sphere, and an examination of how they did so sets the tone for their efforts during the 1990s.

The Senate hearing in 1991 also reveals some of the changing qualities of the world that aided proponents in their attempts to situate the concept and category in scientific, social, and regulatory arenas. As discussed in Chapter 2, the endocrine disruptor concept was undergirded by decades of scientific research and also social

change that helped proponents successfully argue for its relevance in different areas. In particular, the environmental movement made environmental concerns socially prominent and politically actionable. During the early 1990s, though, proponents were especially helped by the regulatory shift away from the cancer paradigm, or the basis of toxic chemicals regulation on cancer endpoints. Increased scientific awareness of noncancerous effects of chemicals in both humans and wildlife came in the 1970s. But the regulatory community's awareness of such things took longer, not coming to the fore until the early 1990s. The regulatory community's growing awareness that developmental and reproductive toxicities needed more regulation presented an opening into which proponents pushed the endocrine disruptor concept and category.

First Introduction to the World: the 1991 Senate Hearing on Reproductive Hazards

In October 1991, the endocrine disruptor concept and category made their first regulatory debut at a Senate hearing on "Government Regulation of Reproductive Hazards" before the Committee on Governmental Affairs (U.S. Congress Senate 1991). Up until the early 1990s, most government regulation of toxic substances focused exclusively on carcinogenesis or acute toxicity as endpoints (U.S. Congress Senate 1991, Testimony of Eleanor Chelimsky). That meant that substances were largely screened only for whether they induced cancer in animal models or whether they resulted in acute poisoning of said animal model. That focus has been called the cancer paradigm and reflected a parallel focus in science on cancer as an endpoint (Ames et. al 1973; Ames, Lee, and Durston 1973; Clayson and Clegg 1991). However, though the scientific

community had begun to move past the cancer paradigm before the 1990s, the regulatory community largely had not.

That began to change in the early 1990s, and the 1991 Senate hearing on the regulation of reproductive hazards was part of that. Ohio Senator John Glenn chaired the Committee on Governmental Affairs and oversaw the proceedings. Glenn, who had been a NASA astronaut before entering politics, started the hearing with a retelling of some historical examples highlighting the need to regulate reproductive hazards, including thalidomide and its associated birth defects,[7] DES and the resulting multigenerational cancers, and the Great Lakes research and early indications of pesticides threat to wildlife (U.S. Congress Senate, 1–2; Vargesson 2015; Herbst and Scully 1970; Colborn et al. 1990). The year 1991 was the thirty-year anniversary of the thalidomide tragedy, and *Great Lakes, Great Legacy?* had been released only a year before. After introducing that history, Glenn then stated the purpose of the hearing: "to assess the actions of the Consumer Product Safety Commission, the Occupational Safety and Health Administration (OSHA), the Food and Drug Administration (FDA), and the Environmental Protection Agency (EPA) to identify and regulate exposures to

[7] Thalidomide was an anti-nausea medication prescribed to women in the 1950s (Vargesson 2015). Somewhere between 10,000 and 20,000 infants exposed to thalidomide *in utero* had severe birth defects like phocomelia (malformation of the limbs) (Vargesson 2015). Though the drug was never approved in the US, the thalidomide tragedy, as it has sometimes been called, changed the way many countries tested and regulated drugs. Thalidomide and its *in utero* effects clearly demonstrated that the development of fetuses could be disrupted with the introduction of certain substances and as such thalidomide is often brought up in the conversations about endocrine disruptors and the regulation of reproductive hazards, though it is not an endocrine disruptor.

reproductively hazardous environmental contaminants" (U.S. Congress Senate 1991, 2–3).

Prior to the hearing proceedings, Glenn had asked the Government Accounting Office (GAO) to investigate whether the regulations of the time adequately protected both humans and wildlife from reproductive and developmental toxins (U.S. Congress Senate 1991, 2). During the 1980s, regulatory agencies became increasingly aware of such toxicities after incidents like the kepone spill in Hopewell, Virginia, and the developing body of work on environmental estrogens led by John McLachlan at the National Institutes of Environmental Health Sciences (NIEHS) (Vogel 2012; Reich and Spong 1983; McLachlan 2016). Glenn's request of the GAO followed in the same vein, given the growing pressure to address reproductive and developmental threats.

As part of the investigation requested by Glenn, the GAO produced a report titled "Reproductive and Developmental Hazards: Regulatory Actions Provide Uncertain Protection" (U.S. Congress Senate 1991, Testimony of Eleanor Chelimsky). The title says it all. The report, though officially authored by Eleanor Chelimsky as Assistant Comptroller General in the Program Evaluation and Methodology Department, was produced by Boris Kachura, Barbara Capman, Robert Copeland, and Kwai-Cheung Chan. The GAO investigated four questions: 1. What chemicals are highly concerning for causing reproductive and developmental diseases?; 2. How are those chemicals regulated?; 3. Are those regulations based on the reproductive and developmental toxicities?; and 4. Are the regulations sufficient? (U.S. Congress Senate 1991, Testimony of Eleanor Chelimsky).

In answer to those questions, the GAO developed a list of thirty chemicals of high concern, including alcohol, lead, DES, the pesticide Mirex (made with kepone), and the class of chemicals called polychlorinated biphenyls (PCBs). Most of the thirty chemicals were regulated by one of the four agencies included in the report. That regulation was largely not due to the reproductive or developmental toxicities of the substances, but instead to the carcinogenicity of the substances. On the whole, the authors of the GAO report concluded that the sufficiency of regulations of developmental and reproductive toxins was in doubt due to the lack of consideration given to reproductive and developmental toxicity data. They ended with a recommendation for a dedicated federal office responsible for compiling data on reproductively and developmentally toxic substances (U.S. Congress Senate 1991, Testimony of Eleanor Chelimsky).

Glenn distributed the GAO's report prior to the hearing, and it played a starring role in many of the testimonies. Those testimonies are revelatory of endocrine disruptor's complex relationship with the cancer paradigm, one of the key barriers to their acceptance as a regulatory concern. Representatives from the four agencies evaluated (and called out) in the report attempted to defend their agency against the accusations leveled against them. The EPA's representative Linda Fisher, the Assistant Administrator for Pesticides and Toxic Substances, stated that "[w]e believe that our actions regarding these chemicals are protective against all endpoints of toxicity" (U.S. Congress Senate 1991, 18). She further claimed that the GAO report provided a "poor basis on which to evaluate the EPA's efforts to protect public health from the effects of the developmental and reproductive hazards" (U.S. Congress Senate 1991, 18). The comments from the FDA representative were much the same, highlighting that the FDA did have testing

protocols in place for evaluating the developmental and reproductive toxicity of chemicals (U.S. Congress Senate 1991, 20).[8]

That was true. Beginning in the late 1970s, both the EPA and the FDA released guidelines for evaluating developmental and reproductive hazards, following the thalidomide and DES incidents. However, as pointed to by the FDA representative Fred Shank, the Director of Food Safety and Applied Nutrition, the agencies, in determining tolerances for chemicals, used the most sensitive endpoints to ensure the lowest tolerance (U.S. Congress Senate 1991, 20). In 1991, and for decades prior, the agencies assumed that cancer was the most sensitive endpoint and thus the one used to set tolerances. Though scientifically, research had called that assumption into question, it was still strongly held by regulatory agencies and thus impeded acceptance of endocrine disruptors as problematic in a regulatory setting because agencies assumed that consumers were already protected against such effects by cancer toxicity testing. That is a key point. In order for endocrine disruptors to be regulated, which meant required testing of hormonal activity and non-cancer endpoints, there needed to be a shift away from the cancer paradigm. The Senate hearing was indicative of the start of that shift, but the testimonies by representatives of regulatory agencies show that proponents still needed to overcome the cancer paradigm to get endocrine disruptors regulated.

Most of the rest of the testimonies at the hearing reaffirmed the findings of the GAO and offered an opportunity to introduce endocrine disruptors to the regulatory

[8] In fact, the comments of all of the representatives' other than the OSHA representative were along the same lines. The OSHA representative, rather than arguing with the conclusions in the GAO report, agreed and highlighted their work with lead as a model for what was needed (U.S. Congress Senate 1991, 23).

community as substances that should fall under the regulation of developmentally and reproductively toxic materials. Both Theo Colborn and Lynn Goldman[9] testified about their own work on the effects of chemicals on reproduction. Goldman discussed the toxic effects of dibromochloropropane (DBCP), while Colborn discussed the research laid out in *Great Lakes, Great Legacy?* (U.S. Congress Senate 1991, Testimony of Theo Colborn and Lynn Goldman). Both researchers' work emphasized the particular threat hormonally active chemicals posed to children. As I discuss in Chapter 6, proponents in the 1990s heavily emphasized the connection between endocrine disruptors and children to solidify the endocrine disruptor category in ways that prompted regulation and social awareness while also picking up on larger social trends.

The Senate hearing served as Colborn's first opportunity to present the recently-formulated endocrine disruptor concept and category. Within her written statement, Colborn discussed the Wingspread work session (U.S. Congress Senate 1991, Prepared Statement of Theo Colborn). She made an explicit argument for the primacy of reproductive effects of chemicals over carcinogenic or acute effects, thereby calling for the abandonment of the cancer paradigm (U.S. Congress Senate 1991, 103). She also called for the redress of the public's lack of knowledge regarding hormonally active chemicals and their exposure, something she herself sought to address following the Senate hearing.

[9] In 1993, Lynn Goldman became the Assistant Administrator for Toxic Substances at the EPA (Krimsky 2000). She was partly responsible for pushing for pesticide legislation reform. At the time of the Senate hearing in 1991, Goldman worked as the Acting Chief of the Office of Environmental and Occupational Epidemiology in the California Department of Health Services (U.S. Congress Senate 1991).

The 1991 Senate hearing on "The Government Regulation of Reproductive Hazards" accomplished several things. It was the first presentation of the endocrine disruptor concept and category, where Colborn made for the first time the argument that endocrine disruptors were scientifically, socially, and regulatorily relevant to an audience other than those who attended Wingspread. In doing so, she set endocrine disruptors on an unusual path. Unlike most science policy issues, proponents of the endocrine disruptor concept and category did not start by trying to gain scientific acceptance or work toward scientific consensus. Instead, their first action after coining the term "endocrine disruptor" was political, a step toward regulating endocrine disruptors when at that point only two dozen scientists even acknowledged that they existed.

The Senate hearing also shows the regulatory reliance on the cancer paradigm, something that needed to change for the regulation of endocrine disruptors. Much of this chapter is about how historical contingencies, changes and movements that started well before the 1990s, helped to create a space for proponents to advance the endocrine disruptor concept and category. The regulatory shift away from the cancer paradigm was one such contingency.

Early Independence from the Cancer Paradigm

The 1991 Senate hearing on the regulation of reproductive hazards was an important step in moving away from the cancer paradigm in toxic chemicals regulation. That step was necessary to the endocrine disruptor concept and category, which relate to chemicals responsible for not only cancer endpoints but also non-cancer endpoints. For regulation of endocrine disruptors, which prioritizes non-cancer endpoints to set

regulatory tolerances, there needed to be an acknowledgement that cancer endpoints did not suffice for toxicity testing. The shift away from the cancer paradigm did not start in 1991 with the Senate hearing after the formulation of the endocrine disruptor concept. It began a decade prior, when reproductive toxicity of chemicals was becoming more apparent as the endocrine disruptor concept developed.

Following the revelations about thalidomide and DES in the 1960s and 1970s, regulatory agencies including the FDA released testing protocols for determining potential reproductive and developmental health outcomes. That work paralleled a scientific shift away from cancer as the most significant endpoint. As discussed in Chapter 2, following identification of the reproductive effects of kepone and other work place hazards, the NIEHS and others began funding developmental and reproductive toxicity research (Vogel 2012). That trend continued in the 1980s, with the founding of a new field on environmental estrogens (McLachlan 1979; McLachlan 1985; McLachlan 2016). Yet, until the 1990s, the cancer paradigm remained supreme. That is especially apparent through a comparison between the 1991 Senate hearing and GAO report and a House hearing and report from a decade prior.

By 1980, Jimmy Carter's Council on Environmental Quality, in conjunction with the EPA, the NIEHS, OSHA, and the National Institute for Occupational Safety and Health (NIOSH), had contracted a science and engineering consulting firm, Clement Associates, to: "research and evaluate the extant scientific, medical and regulatory literature and documents that relate to the effects of chronic exposure to toxic chemicals and their consequence upon human and animal reproductive integrity" (CEQ 1981, iii). In

essence, various federal agencies wanted Clement Associates to investigate the reproductive toxicity of chemicals.

Clement Associates investigated for a year before releasing their report, "Chemical Hazards to Human Reproduction," in 1981. Within their final report (referred to as the CEQ report), the project directors, Ian Nisbet and Nathan Karch, concluded that chemicals may cause a large number of reproductive problems and exposure to such chemicals could be a widespread problem, but that the scientific knowledge at the time was too sparse to justify regulatory action. They analogized the state of the science of reproductive chemical hazards in the 1980s with the state of the science of environmental carcinogens in the 1960s, arguing that more knowledge would help to elucidate the hazards posed by such chemicals and make clear the necessary regulatory program (CEQ 1981, VII-5).[10] With their final report, Clement Associates essentially argued for more scientific research on reproductive toxicities while holding off on recommending regulatory changes.

Just as the GAO report was pivotal in the 1991 Senate hearing, the CEQ report was investigated in depth in a 1982 House hearing on "The Relationship of Exposure to Toxic Chemicals and Reproductive Impairment" (U.S. Congress House 1982). The hearing indicated the federal government's awareness of the potential effects of industrial and agricultural chemicals on reproductive health well before the 1990s. Most of the

[10] Interestingly, the authors of the report expressed doubt that reproductive hazards would be as large of a problem as environmental carcinogens. But they acknowledged that the purpose of their report was, in part, to gather enough information so as to prevent "public controversies," presumably like those environmental carcinogens previously elicited (CEQ 1981, VII-6).

issues brought up in the 1991 Senate hearing and the accompanying GAO report were also discussed at the 1982 House hearing and the CEQ report: the primacy of the cancer paradigm within regulations, the inadequacy of the cancer paradigm to address potential reproductive and developmental concerns, and the need for action of some kind. The major difference being that the action called for in 1982 was scientific research and the action in 1991, regulatory progress.

Perhaps the largest change in the decade between 1980 and 1990 was the increased certainty of researchers that chemicals posed a threat to developmental and reproductive outcomes. That certainty came in part from the research conducted in the intervening decade as the endocrine disruptor concept was developing, by researchers like John McLachlan (McLachlan 1979; McLachlan 1985; McLachlan 2016). Colborn's work in the Great Lakes added to that corpus (Colborn et al. 1990). There were undoubtedly many factors that started to shift attention away from the cancer paradigm in the early 1990s. What matters is that that shift started at a key moment for proponents, who could use the growing awareness of reproductive and developmental hazards to make a case for regulating endocrine disruptors. Throughout the 1990s, proponents continued to fit endocrine disruptors into the reproductive and developmental hazard space opened by the move away from cancer endpoints as the only relevant endpoints. But regardless of the increased certainty and the long awareness of reproductively toxic chemicals, regulatory focus was still very much on cancer. It was the focus of the media. It was the primary concern. The early life of the endocrine disruptor concept and category was marked by the fight by its proponents to make a place for the concept beside carcinogens in regulatory and social settings.

1992: Social Introduction and Continued Focus on Cancer

Because proponents only constructed the endocrine disruptor concept and category in the latter half of 1991, the Senate hearing was the only opportunity for them to begin to push both into various arenas. Proponents' focus in 1991 was regulatory, making a case for the need to regulate endocrine disruptors to policymakers. In 1992, their focus shifted to a second goal: increasing social awareness of the danger posed by endocrine disrupting chemicals.

In 1992, proponents began to use popular media to alert the public of the hidden monster in their pantries and cabinets. In public arenas, proponents of the endocrine disruptor concept also had to push to shift the focus from cancer to reproductive outcomes. In two newspaper articles in 1992, the only two published on endocrine disruptors that year, proponents like Colborn, Michael Fry, and Earl Gray introduced the endocrine disruptor concept and category to a public audience for the first time (Krimsky 2000; Luoma 1992a; Luoma 1992b). In those articles, the researchers made an explicit argument against focus on cancer to an audience who had been focused on the terror of cancer for decades: the American public. The year 1992, as 1991, showed proponents beginning their push of the endocrine disruptor concept and category into different spheres and the various factors that pushed back against them, namely the focus on cancer.

The newspaper articles in 1992 also begin to reveal how actors in different spheres would or would not press back on the concept and category proposed at Wingspread. During the Senate hearing in 1991, Colborn had the opportunity to present her ideas to a regulatory audience and took pains to solidify the endocrine disruptor

concept and category with studies that connected the chemicals with a threat to children, something politically motivating. Throughout the 1990s, the regulatory community only took notice of the endocrine disruptor concept and category when proponents connected them to issues like damage to children and breast cancer. As discussed in Chapter 6, proponents used very specific studies to shore up the concept and category for regulatory audiences, heading off any concerns of lack of substance by providing flashy (if insufficient) substance in the form of scary diseases.

In social arenas, proponents did not need to do that. Throughout the 1990s, popular media willingly accepted the endocrine disruptor concept and category as stories that would sell newspapers. Rarely did popular media publish skeptical articles on the subject. Likely, the willingness of social actors to accept the endocrine disruptor concept and category as presented by proponents derived from the same reasons as regulatory actors: the connection of endocrine disruptors to flashy effects like breast cancer and sperm declines (detailed in the next section). But importantly, proponents did not have to actively hold those connections up in order to garner and keep the attention of social actors. It was much more automatic throughout most of the 1990s, even in the face of pubic obsession with cancer.

Cancer as a Social Obsession

In 1992, the first newspaper article on hormonally active chemicals was published in *The New York Times*. Written by Jon R. Luoma, "New Effect of Pollutants: Hormone Mayhem" appeared in the bottom right corner of the first page of the science section on Tuesday, 24 March 1992 (Luoma 1992a). In the article, Luoma highlighted DES, DDT,

and dioxin as hazardous chemicals for development and reproduction, though he did not mention endocrine disruptors as the overarching category of substances.

Within the article, Luoma featured comments from Colborn, Fry, and Gray, all attendees at Wingspread, as well as McLachlan, a major environmental estrogen researcher. All the researchers noted the animal studies of chemicals like DDT and dioxin, linking those effects with potential human effects. Remember that in 1992, proponents had little, if any, evidence that endocrine disruptors impacted humans. They were reliant on animal studies and extrapolation to humans as well as the flagship example of DES as proof of concept.

Luoma's article started to make a place for the endocrine disruptor concept in the public arena by drawing attention to the potential for chemicals to cause reproductive and developmental abnormalities. The article did not have the hysterical, end of days tone that later popular media articles took with endocrine disruptors. Neither the concept nor the category had gained momentum in 1992, and proponents were still working to make a place for endocrine disruptors beside carcinogens.

Within Luoma's article, that came out clearly. He quoted McLachlan and Colborn as well as Barry Johnson, the Assistant Administrator of the Agency for Toxic Substances and Disease Registry, all of whom called out the regulatory focus on cancer. Johnson went so far as to say: "The focus we've had on cancer is a product of our culture. We find ourselves in this situation because we've given disproportionate attention to the study of cancer as the only risk from environmental hazards because people are frightened by it, and they can understand it. …" (Luoma 1992a, C9). That adequately captures the struggle proponents had in making reproductive and developmental effects

as scary and as relevant as cancerous effects. Throughout the 1990s, that struggle persisted, especially after endocrine disruptors were linked to breast cancer in 1993.

1993: Two New 'Ins' and a Continued Struggle Against Cancer Focus

Both 1991 and 1992 were relatively slow years for the endocrine disruptor concept and category. Throughout, researchers completed little if any scientific study of endocrine disruptors, with proponents focused on introducing their ideas to regulatory and social actors and the rest of the scientific community as yet unintroduced to the concept and category.

That changed in 1993 when three things happened. First, two new studies connected endocrine disruptors to attention-grabbing effects: breast cancer and declining sperm counts (Sharpe and Skakkebæk 1993; Wolff et al. 1993). Those studies, in turn, generated much more public attention on endocrine disruptors and proponents promoted both studies heavily (Healy 1993; Beil 1993; Peterson 1993). Following that increased public attention and acceptance of the endocrine disruptor concept and category, proponents introduced the idea to the scientific community with an article in *Environmental Health Perspectives* (Colborn, vom Saal, and Soto 1993). All three things continued proponents' efforts to make endocrine disruptors scientific, social, and regulatory objects while also showing how social changes and historical trends helped and hindered them in that effort.

Making Room for Endocrine Disruptors Using Fears for Fertility

Luoma's articles in 1992 as well as the long-standing cultural and regulatory focus on cancer make clear that proponents needed to make endocrine disruptors equally terrifying or fascinating to gain social and regulatory attention. In 1993, they got help with that when Nils E. Skakkebæk and Richard M. Sharpe published their article on "Are Oestrogens Involved in Falling Sperm Counts and Disorders of the Male Reproductive Tract?" in *The Lancet* (Sharpe and Skakkebæk 1993). In the article, Skakkebæk and Sharpe discussed research showing that male sperm counts around the world had decreased over the previous thirty years. The authors linked the decrease in sperm to men's increased exposure to estrogenic chemicals and suggested that those chemicals were the cause of the sperm decreases, providing several mechanistic explanations (Sharpe and Skakkebæk 1993, 1395; Sharpe 1993).

Sharpe and Skakkebæk's article was met with tremendous media response. While there were only two articles in 1992 on hormonally active chemicals and their potential effects, there were closer to ten in 1993, many of which discussed the decreasing sperm counts reported in the *Lancet* and came with accompanying scary titles (Krimsky 2000; Luoma 1992a; Luoma 1992b; Healy 1993; Beil 1993; Peterson 1993). Sharpe and Skakkebæk's research helped solidify parts of the endocrine disruptor concept and category by connecting endocrine disrupting chemicals with negative health outcomes that would affect humans around the world. Up until 1993, Colborn and her colleagues relied largely on limited evidence and speculation to link exposure to endocrine disruptors with health effects in humans that might motivate regulation and public

attention. Sharpe and Skakkebæk's article and the attention it received helped to solidify that link, at least in the public's mind.

The connection between declining sperm counts and endocrine disruptors greatly aided proponents in their task of making their concept and category social and regulatory. In the previous two years, proponents struggled against the focus on cancer. Cancer, for most people, is not an abstract disease. Most people know someone who has had cancer and that makes cancer a much realer risk in people's minds. Reproductive and developmental problems, on the other hand, feel more abstract. What is a reproductive problem? Do I know someone who has one? Does it ruin lives the way cancer does? Those questions are not immediately answered for most people when they think about reproductively and developmentally toxic chemicals. So up until 1993, though proponents made social and regulatory actors aware of the threat posed by endocrine disruptors, they failed to inspire any sense of urgency or fear around the chemicals.

Sharpe and Skakkebæk's research changed that. Declining sperm counts worldwide connects the abstract idea of reproductive toxicity to a real impact that leaves men clutching their … chests. The finding fed into social worries about the loss of masculinity and the feminization of the industrialized world. Sperm declines also pick up on perhaps the longest running human obsession: sex. Articles about sperm sell newspapers, which means that the study and its link to endocrine disruptors gained attention just due to the headlines. For social actors, without much help from proponents, it solidified the endocrine disruptor concept and category as real problems that needed to be addressed—and written about more in popular media.

For regulatory actors, proponents used the finding to solidify what counted as an endocrine disruptor. As discussed in more detail in Chapter 6, the concept and category proposed in 1991 lacked specific details in terms of what counted as an endocrine disruptor. The scientific community pushed back on the lack throughout most of the 1990s (see Chapter 4). Though proponents attempted to use the Sharpe and Skakkebæk study with scientific audiences, it largely fell flat due to the scientific problems with the study and the fact that it was largely speculative (Saidi et al. 1999; Olsen et al. 1995; Safe 1994; Safe 1995). The study did not actually clarify what counted as an endocrine disruptor. But with regulatory audiences, proponents controlled the presentation of the study in such a way that they were able to use it to solidify their category in a way that spurred regulatory action. Throughout the 1990s, proponents collected several key studies, the sperm count study being one, that they used to answer the question of what an endocrine disruptor is for regulatory audiences. In the first Senate hearing in 1991, Colborn started that work, linking endocrine disruptors to damage in children (U.S. Congress Senate, Testimony of Theo Colborn). In later hearings, proponents relied on Sharpe and Skakkebæk's work (U.S. Congress 1993; U.S. Congress House 1993; U.S. Congress House 1995a; U.S. Congress House 1995b). Between the two, they answered what are endocrine disruptors sufficiently for policymakers.

However, though the finding that sperm counts were declining worldwide greatly helped proponents sell the endocrine disruptor concept and category to social and regulatory audiences, their use of it was not without cost. In popular media, journalists linked sperm count declines to estrogenic chemicals, in particular, as well as other findings about the feminization of fish and amphibians exposed to the same chemicals.

Through that, the public spotlight shone more on estrogenic chemicals than on endocrine disruptors more broadly. The same process occurred in regulatory settings as proponents relied more and more on feminizing effects of endocrine disruptors to prompt regulatory action (see Chapter 6). One consequence of that focus was that in the 1996 legislation, Congress only mandated an estrogenic substances screening program, rather than an endocrine disruptor screening program. Ultimately, the Endocrine Disruptor Screening Program was put in place, due to proponents' work inside the EPA.

Stealing the Spotlight: Breast Cancer

The remaining popular press articles published in 1993 focused on a second study that linked endocrine disruptors to a human disease: breast cancer. Several studies published in 1993 found elevated levels of organochlorines (PCBs and DDT, most notably) in the blood and tissue of women with breast cancer, leading some to postulate that exposure to such estrogenic compounds was the cause of breast cancer, especially given the increased rates of the disease (Wolff et al. 1993; El-Bayoumy 1992; Davis et al. 1993). Most notably, Mary Wolff and her colleagues used close to 15,000 samples from New York University's Women's Health Study to make that link (Wolff et al. 1993). The link between endocrine disruptors and breast cancer gained widespread public attention in newspaper articles, given that it picked up on an increased perception of breast cancer risk during the 1990s. The study also featured prominently in a House hearing in 1993.

In October of 1993, the House Subcommittee on Health and the Environment held a hearing on "Health Effects of Estrogenic Pesticides," presided by Henry A. Waxman, who started the hearing by noting, "[t]oday we are holding the first Congressional hearing

on a topic of potentially far-reaching significance for environmental health, pesticides that imitate human hormones, particularly the female hormone estrogen" (U.S. Congress House 1993, 1). Waxman continued to note the three major findings of the hearing: 1. That estrogenic compounds had been linked to health and environmental mal-effects, 2. That such compounds had been found in the food supply, and 3. That the EPA did not screen for estrogenic activity. He then promised to work toward legislation that would require such screening, before largely confusing his message by stating (for the parents and consumers listening in) that the effects of hormonal pesticides were not proven, that consumers should not panic (U.S. Congress House 1993, 1).

The testimonies from the hearing largely, if not entirely, focused on breast cancer. Though many of the scientists present, including Goldman, Colborn, McLachlan, and Ana Soto, all focused their statements on the numerous effects endocrine disruptors could have, the questions fielded by those researchers were about breast cancer (U.S. Congress House 1993, Testimony of Lynn Goldman, Theo Colborn, John McLachlan, and Ana M. Soto). Interestingly, though Waxman derided the EPA for their focus only on cancer endpoints in his introduction, the entire hearing focused on a single cancer endpoint. That is demonstrative of endocrine disruptors' complicated relationship with cancer and the cancer paradigm.

On the one hand, endocrine disruptors can cause cancer, as in the case of DES and clear cell adenocarcinoma of the vagina, and the connection between breast cancer and endocrine disruptors drove the eventual regulation of endocrine disruptors (Herbst and Scully 1970; see Chapter 6). Proponents heavily cited Wolff's study in their Congressional testimony as a way to further solidify the endocrine disruptor concept and

category (see Chapter 6). In conjunction with effects in children and sperm declines, proponents used conspicuous effects of endocrine disruptors to obfuscate that the concept and category lacked important specifics, meaning that regulatory and social actors largely accepted both constructs without deep probing.

On the other hand, cancer, and breast cancer in particular, tended to overshadow endocrine disruptors in the 1990s. During the early years, regulatory and social focus was on cancer endpoints and proponents had to fight to make a place for reproductive and developmental endpoints. As the 1990s continued, proponents' heavy use of Wolff's study helped them, but also put the focus back on cancer. It is not unfair to say that endocrine disruptors were regulated in 1996 as a way to combat rising breast cancer rates (see Chapter 6). In that way, the connection between breast cancer and endocrine disruptors served some of the goals of proponents, in that endocrine disruptors did get regulated. But it hindered their goal of increasing public awareness of endocrine disruptors as ubiquitous chemicals that could cause a wide range of negative effects in humans. It also added to the emphasis on estrogenic chemicals, rather than all hormonally active chemicals, which had consequences for regulation.

An Announcement to the Scientific Community

The same year as the House hearing and the revelations about sperm counts and breast cancer, proponents introduced the endocrine disruptor concept and category for scientific actors. Up until 1993, proponents' focus was on regulatory and social actors, rather than scientific ones. They did not first seek scientific buy-in before taking their ideas to society. Proponents largely ignored the opinions of the scientific community

throughout the 1990s if they did not serve their goals of increasing public awareness and generating regulatory action. In the early 1990s, little research dealt specifically with endocrine disruptors, the term appearing in fewer than three scientific publications at that time. Research continued on environmental estrogens, a holdover from work in the 1980s, but endocrine disruption remained a fringe idea by virtue of the fact that proponents spent little time alerting scientists to their thoughts. In 1993, supporters of the endocrine disruptor concept attempted to rectify that.

In 1993, Colborn, Soto, and vom Saal detailed the endocrine disruptor concept in "Developmental Effects of Endocrine-Disrupting Chemicals in Wildlife and Humans" in *Environmental Health Perspectives* (Colborn, vom Saal, and Soto 1993).[11] The seven-page article was essentially a recapitulation of the endocrine disruptor concept from the Wingspread consensus statement. The authors laid out environmental health effects seen in wildlife exposed to endocrine disrupting chemicals and then followed with a discussion of DES as a "model for exposure to estrogenic chemicals in the environment" (Colborn, vom Saal, and Soto 1993, 379). Colborn, Soto, and vom Saal, like in the Wingspread consensus statement, relied heavily on DES as the bridge between wildlife effects and potential human effects, which remained largely undocumented in 1993 (and in 2018).

Colborn, Soto, and vom Saal's article directing scientific attention to the endocrine disruptor concept and category, on top of the growing public and regulatory attention on the idea, launched widespread study of the substances. In the years

[11] *Environmental Health Perspectives* became the journal where many articles on endocrine disruptors were/are published. It is supported by the NIEHS.

following, more researchers entered the endocrine disruptor space and found the concept and category lacking. Where social actors accepted both constructs at face value, and where the perceptions of regulatory actors were tightly controlled by proponents during Congressional hearings, scientific actors strongly pushed back at the concept and category and found both lacking. This is explored fully in Chapter 4.

1994: Scientific Limbo and Media Attention

In 1994, proponents had to grapple for the first time with pushing the endocrine disruptor concept and category into the scientific community. Following their 1993 article where they laid out the concept for a scientific audience, more researchers began probing proponents' ideas and evidence and found them lacking. Beginning in 1994, scientific views on the endocrine disruptor concept and category began to create a spectrum, ranging from proponents of the concept who viewed the idea as proven and immediately actionable to strong skeptics who viewed what they called the hypothesis as critically lacking and deserving of little attention or action. Those groups made up the minority, with most researchers sitting somewhere in the middle, spending their time and research dollars seriously investigating the missing pieces of the endocrine disruptor concept and category. That spectrum, and the different views on the concept and category, drove scientific research on endocrine disruptors through the 1990s.

While that spectrum developed, and proponents attempted to situate their ideas in a scientific context, social actors continued their work hyping the endocrine disruptor concept as a public health catastrophe. Their coverage of endocrine disruptors in 1994 is demonstrative of the tradeoffs proponents made in using particular evidence to argue for

the social relevance of the concept and category. In previous years, proponents relied on studies linking endocrine disruptors to sperm count declines and breast cancer. Then, in 1994, another study linked endocrine disruptors to shrinking alligator penises in Florida (Guillette et al. 1994). All three studies made for gripping news, but proponents were not able to control the popular media's spin on the findings, which revolved around the loss of or attack on masculinity and emphasized estrogenic actions of endocrine disruptors. By the end of 1994, proponents had accomplished two of their goals, increasing public awareness of endocrine disruptors and sparking scientific investigation of them, but not in the way they intended.

The Scientific Community's Lack of Acceptance

The article on the endocrine disruptor concept by Colborn, vom Saal, and Soto, published at the end of 1993, did not lead to a widespread scientific acceptance of the concept in 1994. When the three proponents laid out their concept and category in 1993, they used the same argument and evidence they used in 1991, when initially proposing the idea. They first laid out the endocrine disruptor concept, the two-part idea that chemicals with the ability to interfere with hormone action to cause negative effects exist, and that those chemicals threaten the health of humans and wildlife. Colborn, vom Saal, and Soto also included a description of the endocrine disruptor category, outlining three criteria: the effects of endocrine disruptors differ based on the time of exposure, can impact the development and reproduction of organisms exposed, and may manifest years after initial exposure (Colborn, vom Saal, and Soto 1993, 378).

They then relied heavily on Colborn's and others' research in the Great Lakes to demonstrate the wide range of effects endocrine disruptors can have before using the example of DES to bridge the effects seen in wildlife with the potential effects in humans (Colborn, vom Saal, and Soto 1993, 379). The article ends with a section titled "Characterization of Endocrine-Disrupting Chemicals," in which the authors listed a series of things that endocrine disruptors have done, like accumulating in human tissues and causing proliferation in breast cancer cell lines, without actually characterizing the chemicals. The authors failed to address how to identify an endocrine disruptor, how an endocrine disruptor works, or what counts as an endocrine disruptor.

In that way, the argument Colborn, vom Saal, and Soto laid out for the scientific community was almost exactly the same as the one they used for regulatory and social audiences. Just as with non-scientific audiences, proponents relied on conspicuous studies that showed dire effects of endocrine disruptors to make the point that such chemicals threaten human and wildlife populations and should be acted upon scientifically, socially, and politically. But where social actors readily accepted that narrative, and the perceptions of regulatory actors could be controlled by the reinforcement of certain evidence during Congressional hearings, scientific actors probed deeply at the large claims proponents made.

In 1994, more researchers entered the endocrine disruptor space, with increased funding for endocrine disruptor research from organizations like the EPA and the W. Alton Jones Foundation (Krimsky 2000, 24). Those researchers addressed not only the evidence and claims proponents used in their 1991 and 1993 publications, but also the evidence and claims they were using in social and regulatory contexts. In 1994, Stephen

Safe, one of the most skeptical researchers of the endocrine disruptor concept, published an opinion piece in *Environmental Science and Pollution Research International* (Safe 1994). In the article, Safe called out the hysteria generated over studies linking estrogenic chemicals[12] to breast cancer and sperm count declines, pointing to scientific issues with the research while also advancing a counter argument about the threat posed by such chemicals. Safe, like many researchers after him, pointed to the very low level of chemicals most humans are exposed to as a reason to downgrade the threat posed by endocrine disruptors while also noting the wide variety of hormonally active substances humans have always been exposed to argue that perhaps all the effects balance out (Stone 1994; Safe 1994; Safe 1995).

In his article, Safe clearly picked up on the wider arguments proponents were making to get endocrine disruptors regulated, pushing back on their social and regulatory arguments as well as their scientific ones. As detailed more fully in Chapter 4, by 1994 proponents had succeeded in making the endocrine disruptor concept and category scientific, social, and regulatory in so far as actors from each sphere could not separate those aspects to comment on one. Throughout the 1990s, scientific researchers treated the endocrine disruptor concept as a tripartite idea, rarely commenting only on the scientific validity of the idea rather than its validity and what actions should be taken based on that validity (see Chapter 4). During 1994, scientific actors began to develop a large number

[12] Safe rarely, if ever, used the term "endocrine disruptor" in his writing, except in a pejorative sense. However, when referring to hormonally active chemicals or estrogenic chemicals, it is clear he is speaking about endocrine disruptors and the work of proponents.

of different opinions on those questions, something that would impact the continued trajectory of the concept and category.

Endocrine Disruptors as Attacking and Assaulting in the Media

As the scientific community began paying attention to the concept and category, popular media increased their attention. The year 1994 saw a six-fold increase in the number of popular articles on estrogenic chemicals and endocrine disruptors (Krimsky 2000). The articles carried a distinct sense of dread, worry, and fear. While many still focused on breast cancer as the main terror of estrogenic chemicals, far more had taken the reported decrease in sperm counts and the estrogen like actions of chemicals to spin a new story: the distortion of sex (Cone 1994a; Cone 1994b; Cone 1994c; Begley and Glick 1994; Stevens 1994). Many of the articles published in 1994 had titles like "Gender Warp: Sexual Confusion in the Wild," "Chemicals Tinker with Sexuality," or "Something is Attacking Male Fetus Sex Organs," with accompanying lines reading something like "Sperm counts down? Penises shriveled? Hey, Rush, don't blame it on feminists. It may be from chemical pollutants in water and food" (Cone 1994a; Cone 1994b; Cone 1994c; Begley and Glick 1994; Goodman 1994). In fact, while some articles talked about the ability of chemicals to masculinize females, the large majority focused on feminization and disappearance of males.

That trend only increased after the publication of Louis Guillette's research on alligators near superfund sites in Florida. Guillette and his team found that alligators exposed to estrogenic chemicals presented with hormonal fluctuations and reproductive problems. Most especially from a popular media perspective, Guillette found that the

penises of male alligators were shrinking. Many newspapers and morning shows picked up on Guillette's study, and the combination of breast cancer, sperm declines, and shrinking penises heightened public awareness of endocrine disruptors. During 1994, proponents clearly achieved their goal of increasing public awareness of endocrine disruptors and the problems they pose, but perhaps not in the ideal way. In the scientific community, proponents succeeded in intensifying scientific study of endocrine disruptors but only in the face of widespread disagreement with their claims. Similarly, in the social arena, impactful studies on shrinking penises and breast cancer assisted proponents in bringing awareness, but drew attention to only small parts of the endocrine disruptor concept and category, the connection to cancer and the effect on males. Both drew attention away from what proponents saw as the much larger problem, the wide range of effects from all hormonally active chemicals, not just the two effects from estrogenic chemicals.

However, proponents continued to use conspicuous studies that advanced their goals, while also undercutting their point. In 1994, the British Broadcasting Corporation (BBC) released a documentary title *Assault on the Male* (BBC 1994). Though the film was largely a flop, airing only two times on the Discovery Channel over Labor Day weekend to an audience of perhaps 500,000 households, the film found critical acclaim (Krimsky 2000, 64). It won both a British Environment and Media Award as well as an Emmy Award for "Outstanding Information or Cultural Program" (Krimsky 2000, 64). In the film, individuals discuss several scientific discoveries that led to the endocrine disruptor concept, including the shrinking penis size of Florida alligators and the hermaphroditism in fish near sewer outfalls, connecting both to what the film called real

changes in human reproduction. Supporters of the endocrine disruptor concept distributed the BBC film to policymakers and scientists to push their agenda of getting endocrine disruptors regulated (Krimsky 2000, 64).

The increased scientific and social attention on endocrine disruptors in 1994 shows the success proponents had with pushing the endocrine disruptor concept and category into different arenas. It also shows the varied push back they got from actors within those arenas. Scientific actors picked up on weaknesses in the concept and category, strongly rejecting the certainty and call for action proponents projected. That contributed to endocrine disruptors' unique path to regulation, which occurred in the midst of scientific dissent. Social actors also pushed back, in so far as social trends and the spin popular media placed on studies used by proponents drew attention away from the much larger point proponents were trying to make. Ultimately, the social attention and the trends that attention played into were instrumental in getting endocrine disruptors acknowledged, by the public and regulators, but it did push back on some of what proponents tried to do in the 1990s.

1995: A Regulatory Place and Growing Scientific Dissent

In 1995, proponents used their last opportunity to achieve their goal of endocrine disruptor regulation. In previous years, proponents testified at Congressional hearings on the endocrine disruptor concept and the need to act on hormonally active chemicals, but they were fighting an uphill battle against reliance on the cancer paradigm and the general inertia of the US regulatory system. That changed in 1995 as a historical contingency came to a head. In 1995, Congress was faced with the decision to either

revamp the chemical regulation system in the US or see the demise of the US agricultural industry. Because of that, policymakers were much more focused on passing a bill that would change chemical regulations, a bill that proponents could try to attach endocrine disruptor regulation to. That window of opportunity, discussed in more detail in Chapter 6, created a potential space for endocrine disruptors in the regulatory world that proponents took advantage of by continuing their reliance on a small number of conspicuous scientific studies in regulatory settings.

Amid that effort by proponents, the scientific community continued to grapple with endocrine disruptors. Research on the substances greatly expanded, but no studies had firmly answered the lingering questions many had: what counts as an endocrine disruptor, how do endocrine disruptors work, do endocrine disruptors pose a threat to human populations? Those questions came out in a number of meetings and consensus reports on endocrine disruptors, which focused on a central question: What is the definition of endocrine disruptors? By the end of 1995, an agreement had not been reached, even as regulation of endocrine disruptors progressed, a divide that would have far reaching implications.

A Changing World with a Space for Endocrine Disruptors

While the media hyped the threat posed by endocrine disruptors and the scientific community interrogated the substances, the regulatory community began to make room for endocrine disruptors and the endocrine disruptor concept in 1995. Regulators did that not by acknowledging the problem endocrine disruptors posed, but by acknowledging a much older problem: the Delaney Clause and pesticide testing in the US.

For most of the 1990s, members of Congress had been proposing bills to overhaul the pesticide testing requirements in the US (H.R. 4739 100th Cong.; H.R. 1725 101st Cong.; S. 2875 100th Cong.; S. 722 101st Cong.; H.R. 2342 102nd Cong.; S. 1074 102nd Cong.; H.R. 2597 102nd Cong.; H.R. 3216 102nd Cong.; S. 331 103rd Cong.; H.R. 872 103rd Cong.; S. 1478 103rd Cong.; H.R. 4091 103rd Cong.; S. 2084 103rd Cong.; H.R. 4362 103rd Cong.; H.R. 1627 104th Cong.). Those proposals were not due to any feeling that the current system was underperforming, but rather because Congress had been backed into a regulatory corner. In 1958, Congress passed an amendment to the 1938 Food, Drug, and Cosmetic Act (Pub. L. 75–717, 21 USC § 301 et seq.). The 1958 Food Additives Amendment contained what would be the thorn in pesticide regulators' sides for nearly thirty years: the Delaney clause. Suggested by representative James Delaney,[13] the chairman of the committee tasked with investigating the use of chemicals in food production, the Delaney clause stated that, "[n]o additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal …"[14] (52 Stat. 1041-1785). Most, if not all, chemical substances on Earth can be shown to cause cancer under the right circumstances. As was clear to many at the time of its passage, that meant that the Delaney clause essentially disallowed the approval of any chemical (Degnan and Flamm 1995, 237).

[13] Delaney also worked to pass a ban on switchblade knives.

[14] The Delaney clause applied to food additives, which was broadly enough defined to include the residues of pesticides left in foods (Merrill 1997, 319).

Given that (rather large) issue, the FDA and EPA (after its creation in 1972) did not strictly enforce the Delaney clause. Instead, both agencies followed a tolerance setting model whereby they determined the maximum amount of a given pesticide that could safely remain in food (Committee on Pesticide Use Patterns 1987). Though everyone was aware that that approach did not satisfy the mandate of the Delaney clause, which called for zero tolerance, it was a more practical application. But it generated extreme controversy.[15] The FDA's and the EPA's applications of the clause was challenged regularly throughout the 1970s and 1980s (*Environmental Defense Fund, Inc. v. DHEW* 1970; *Environmental Defense Fund, Inc. v. Ruckelshaus* 1971; *Chemetron Corp. v. DHEW* 1974; *Hess & Clark, Division of Rhodia, Inc. v. FDA* 1974; *Rhone-Poulenc, Inc., ETC. v. FDA* 1980; *Scott v. FDA* 1984; *Public Citizen v. DHHS* 1986; *Public Citizen v Young* 1987; *Public Citizen v. Bowen* 1987; *Simpson v. Young* 1988; *Nader v. EPA* 1988). For the most part, the court decisions emerging from those challenges had relatively little effect on the actions of either agency.

That changed in 1992, when the Ninth Circuit US Court of Appeals decided that the EPA's approval of four pesticides violated the Delaney clause, thus necessitating the EPA revoke approval for four widely used agricultural pesticides—benomyl, mancozeb, phosmet, and trifluralin (*Les v. Reilly* 1992). The Ninth Circuit's decision set a precedent that the EPA must strictly enforce the Delaney clause.

[15] Interestingly, the main locus of the controversy around the application of the Delaney clause was the use of DES in livestock. DES was used widely as growth hormone in both beef and poultry. Eventually, Congress passed the DES proviso, which excepted DES from the Delaney clause (Marcus 1994, 65).

The 1992 case *Les v. Reilly,* along with the many challenges to the Delaney clause where courts could do little but point to the clear language of the clause itself, backed Congress into a corner where they either had to pass a bill revising the Delaney clause or risk revocation of approval for the pesticides required to maintain the nation's agricultural enterprise. Bills began appearing in the early 1990s, many with the title of "Food Quality Protection Act" (H.R. 4739 100th Cong.; H.R. 1725 101st Cong.; S. 2875 100th Cong.; S. 722 101st Cong.; H.R. 2342 102nd Cong.; S. 1074 102nd Cong.; H.R. 2597 102nd Cong.; H.R. 3216 102nd Cong.; S. 331 103rd Cong.; H.R. 872 103rd Cong.; S. 1478 103rd Cong.; H.R. 4091 103rd Cong.; S. 2084 103rd Cong.; H.R. 4362 103rd Cong.; H.R. 1627 104th Cong.). The bills proposed very much focused on dismantling the Delaney clause and contained no mention of hormonally active substances.

Fortunately, or unfortunately, the corner Congress was occupying got much smaller by 1995, when the decision in *California v. Browner* became clear and they were handed a time frame in which they must pass changes to the Delaney clause (*California v. Browner* 1994). In the case, the state of California challenged the EPA's application of the Delaney clause. The court's decision, which was apparent long before the end of the case, required the EPA to revoke approval for any previously approved carcinogenic pesticide by 1997 (*California v. Browner* 1994). That list of pesticides would have included thirty-six of the most common pesticides used on crops in the US (Cushman 1994). Essentially, the result of the case signaled to Congress that if they did not change the Delaney clause by 1997, most agriculture in the US would grind to a halt (Merrill 1997; Cushman 1994). Proposed changes to the Delaney clause were taken much more seriously.

That created an opportunity for proponents of regulating endocrine disruptors. By 1995, they knew that a bill was going to pass to update chemical testing in the US. They also knew that they had sympathetic policymakers who could be convinced to include a section on endocrine disruptor regulation in the bill. Those policymakers had been cultivated by proponents in previous Congressional testimonies and in other outreach (U.S. Congress Senate 1991; U.S. Congress 1993; U.S. Congress House 1993; Krimsky 2000). They included Henry Waxman, a California Representative who had overseen several hearings on reproductive and developmental toxicities in the preceding years and was familiar with, and sympathetic to, regulating endocrine disruptors as a result. Friendly policymakers also included Alfonse D'Amato, a Senator from New York who was particularly interested in regulating endocrine disruptors as a way to head off rising breast cancer rates (U.S. Congress 1993, Testimony of Alfonse D'Amato).

Waxman and D'Amato are proof of the effectiveness of proponents' techniques in earlier years to push the endocrine disruptor concept into the regulatory arena. From 1991 to 1995, proponents carefully controlled the scientific narrative about endocrine disruptors presented to policymakers, highlighting studies linking the chemicals to breast cancer and sperm declines. In doing so, they presented endocrine disruptors as regulatory problems that could be acted upon to address effects that policymakers' constituents cared about, something proponents had also worked to ensure through their interviews with popular media. This is discussed more in Chapter 6. So, by 1995, there was space for the endocrine disruptor concept in regulation. Proponents only needed to capitalize on it.

The Last Argument for Endocrine Disruptor Regulation

In May of 1995, around three months after the end of *California v. Browner*, Thomas J. Bliley Jr. introduced the Food Quality Protection Act of 1995, which would eventually pass and include the regulation of endocrine disruptors (H.R. 1627 104th Cong.). The bill had ninety-seven cosponsors from both sides of the aisle and made no mention of endocrine disruptors, estrogenic pesticides, or hormonally active substances (H.R. 1627 104th Cong.). Their potential place within the bill, as substances with effects that should be tested for regularly, was not guaranteed. The Food Quality Protection Act of 1995 focused on modifying the Food, Drug, and Cosmetic Act to eliminate the problem of the Delaney clause and largely allow the EPA and FDA to continue as they had. The bill was immediately referred to the House Agriculture Subcommittee on the Department of Operations, Nutrition, and Foreign Agriculture (referred to as the Agriculture Subcommittee), which held a hearing on 16 May 1995 (U.S. Congress House 1995a).

No endocrine disruptor concept proponents attended the hearing, nor were any invited to testify. Endocrine disruptors came up one time at the hearing, in the testimony of Jay Feldman, Executive Director of the National Coalition Against the Misuse of Pesticides. Feldman acknowledged freely that he was "a minority voice" in the hearing but that he represented "a majority of views in terms of the world of public opinion" (U.S. Congress House 1995a, Statement of Jay Feldman). Feldman clearly recognized the increasing media attention paid to the endocrine disruptor concept and the fear that attention had engendered of the chemicals. Feldman argued that the Agriculture

Subcommittee should examine endocrine effects and seek to ensure that the bill addressed such issues.

Goldman, who at that point had made her way to the EPA, also testified. She did not refer to endocrine disruptors, but highlighted the need to focus on non-cancer endpoints in setting tolerances. Her testimony illustrates the continued emphasis on cancer in a regulatory setting. In previous years, proponents struggled to turn focus to non-cancer endpoints in regulation. In social spheres, they successfully drew attention away from cancer through sperm and penises, though still using the connection between breast cancer and endocrine disruptors as a key touchstone. Proponents attempted to do the same in regulatory settings, but as Goldman's testimony shows, it was not clear in 1995 how successful they were. Many policymakers still focused on cancer, as did the initial Food Quality Protection Act (U.S. Congress House 1995a; H.R. 1627 104th Cong.).

A little over ten days after the Agriculture Subcommittee held its hearing, a second subcommittee held a hearing on the same bill (U.S. Congress House 1995b). The House Commerce Subcommittee on Health and Environment convened on 29 May 1995 to once again discuss the Food Quality Protection Act of 1995. The focus of that hearing was also on modifications to the Delaney clause and a new pesticide threshold setting technique generally, but endocrine disruptors appeared more prominently (U.S. Congress House 1995b). Feldman once again testified on behalf of the National Coalition Against the Misuse of Pesticides, deriding the proposed bill for not accounting for non-cancer endpoints, especially endocrine disrupting endpoints (U.S. Congress House 1995b, Testimony of Jay Feldman). Erik Olson testified on behalf of the National Resources Defense Council, and his written testimony repeatedly discussed endocrine disrupting

chemicals and the lack of protections against them (U.S. Congress House 1995b, Statement of Erik Olson).

Both hearings on the Food Quality Protection Act show the continued effort by proponents to get regulatory buy-in for the endocrine disruptor concept and category. Though proponents played a smaller role at the final two hearings, they continued to work behind the scenes to get endocrine disruptors regulated, shoring up the concept and category in specific ways for policymakers. However, by the end of 1995, the effects of proponents' work were not obvious in so far as the final language of the Food Quality Protection Act had not been determined. Proponents had to wait.

Science Grapples with Endocrine Disruptors

As the regulatory community made a space for endocrine disruptors, or perhaps more accurately endocrine disruptors filled a space made by other issues, the scientific community continued to push back on the endocrine disruptor concept and category. Skeptics of the ideas continued to write scathing opinion pieces, calling into question all of the claims made by proponents. Most the scientific community, meanwhile, continued to try to solidify what an endocrine disruptor was, or could be, or whether the entire study of them should be dropped.

In April of 1995, the EPA hosted a work session on the health and environmental effects of endocrine disruptors, led by Robert Kavlock (Kavlock et al. 1996). The statement that came out of the session encapsulates much of the continued scientific disagreement over the endocrine disruptor concept and category. The main conclusion

from the work session was that what they called the endocrine disruptor hypothesis[16] "was of sufficient concern to warrant a concentrated research effort," presumably to determine the validity of the hypothesis (Kavlock et al. 1996, 733). In his report on the workshop, Kavlock noted that the studies at the time were "inadequate for quantitative risk assessment" and he emphasized the necessity of the Bradford Hill criteria to determine if there was truly a connection between endocrine disrupting chemicals and adverse health outcomes (Kavlock et al. 1996). The EPA work session, which brought together close to ninety experts, called for further research to reduce uncertainty with the endocrine disruptor concept: namely, questions of what endocrine disruptors were and whether such substances truly did pose a problem for humans.

That message is quite a bit different from the one proponents presented in hearings before Congress. While endocrine disruptor concept supporters told members of Congress that the concept and category were fully valid and ready for regulation, the rest of the scientific community maintained that the concept and category needed more investigation to make any determination regarding the regulation of endocrine disruptors. In all actuality, during the 1990s, proponents made relatively little effort to promote their ideas within the scientific community. Instead, proponents focused on their work with social and regulatory audiences, not calling for scientific consensus until 1998 (Colborn 1998a). Proponents like Colborn clearly made efforts to solidify the concept and category for social and regulatory actors by connecting endocrine disruptors with attention-

[16] Scientific critics of the endocrine disruptor concept proposed in 1991 generally referred to the concept as the endocrine disruptor hypothesis, demonstrating their lack of confidence in the claims (Safe 1994; Safe 1995; Kavlock et al. 1996; Stone 1994). This is explored in more depth in the next chapter.

grabbing diseases and effects like breast cancer and shrinking penises. For those audiences, that tactic was successful. Proponents tried to use the same tactic with scientific audiences, relying on studies connecting endocrine disruptors with serious effects in humans and wildlife while ignoring some of the basic knowledge about endocrine disruptors that remained uncertain.

The failure of that tactic became clearer as the 1990s progressed. In 1995, the EPA, the Centers for Disease Control and Prevention (CDC), the Department of the Interior (DOI), and Congress requested that the National Research Council evaluate what they called the endocrine disruptor hypothesis (NRC 1999). The National Research Council was meant not only to review the literature on hormonally active substances, but also to identify uncertainties, recommend research, and establish a "science-based conceptual framework for assessing observed phenomena" (NRC 1999, ix). Though the Council did not publish their report until 1999, its content is equally informative of the scientific mindset in 1995. The report concluded that,

> …[*L*]*imitations and uncertainties in the data could lead to different judgments* among committee members with regard to interpreting the general hypothesis, determining appropriate sources of information, evaluating the evidence, defining the agents of concern, and evaluating environmental and biologic variables.
>
> *Some of the differences reflect areas where additional research would help; others reflect differing judgments about the significance of the existing information.* The differences are not confined to this committee but are reflected in the scientific community at large. Some differences appear to stem from

> different views of the value of different kinds of evidence obtained by experiments, observations, weight-of-evidence approaches, and extrapolation of results from one compound or organism to others, as well as allowable sources of information and criteria for arriving at meaningful conclusions and recommendations (NRC 1999, 2) (emphasis added).

What the report makes clear is that the endocrine disruptor concept was very much disputed. The dispute centered on the lack of certain kinds of evidence, like evidence of negative health outcomes in humans, but also around the uncertain meaning of some of the evidence used (see Chapter 4). The evidence available at the time, mostly deriving from animal research, could be interpreted in a number of ways. As the authors of the NRC report note, scientists hotly debated whether certain findings, like declining sperm counts, actually meant that endocrine disruptors threatened human health or whether the declining sperm counts worldwide were a statistical artifact. The largest looming question for the endocrine disruptor concept remained whether data could be extrapolated to human populations.

Scientists did not buy in to the endocrine disruptor concept or category in 1995. Many researchers continued to investigate hormonally active chemicals, their characteristics, effects, and mechanisms of action, but that did not lead to scientific consensus. By the end of 1995, scientific disagreement over the endocrine disruptor concept had only grown, with a wider range of opinions on the claims made and action called for by proponents. That feature is part of what makes endocrine disruptors so interesting. Most science policy issues begin with scientific consensus, a broad agreement that something poses a threat or needs to be acted upon. Then, a case is made for

regulation, during which a vocal minority who disagrees gets amplified in the media stalling any regulatory progress. Endocrine disruptors flip that narrative, rapidly getting regulated amidst widespread scientific dissensus and the amplification of a vocal minority pushing for regulation. How that process occurred is the focus of this chapter, while the following chapters details why it was successful.

1996: Regulation in the Face of Scientific Disagreement

In 1996, proponents attained their goal of seeing endocrine disruptors regulated with the passage of the Food Quality Protection Act. The majority of the Act changed the approval process for chemicals in the US broadly, but one small section called on the EPA to screen new chemicals for hormonal activity. The 1996 Act really was the culmination of one line of proponents' work in the 1990s, to see to the regulation of endocrine disruptors. Their efforts in prior years, focusing on presenting a specific narrative to regulators combined with intense efforts to make endocrine disruptors a social concern, led to their success. However, the tactics they used impacted the language of the final Act as well as the work proponents had to keep up after its passage.

The year 1996 also saw two publications that played roles in the continued scientific discussion of the endocrine disruptor concept. One publication, an article published by McLachlan's lab on the effects of endocrine disruptors at low doses, could have served as a foundation for building scientific consensus. It addressed one of the main issues scientists continued to have with the concept: that humans are exposed to very little amounts of endocrine disrupting chemicals and therefore those chemicals could

not have a large effect. As detailed in the next section, the foundation McLachlan's paper could have served as crumbled.

The same year, Colborn and two colleagues published a full-length popular book on the endocrine disruptor concept, laying out their evidence and thought process going into the 1991 creation of the concept and some steps they think every person should follow to reduce their exposure to endocrine disrupting chemicals. The book, *Our Stolen Future*, and its reviews demonstrate the continued differences in actors' responses to the endocrine disruptor concept and category. Public audiences loved the book, and it received high praise in publications like *Los Angeles Times* (Meadows 1996; Kamrin 1996; Lemonick 1996; Lee 1996; Krimsky 2000). Reviewers in scientific publications like *Science* took a rather dismal view of the work, calling attention to the scientific uncertainty around endocrine disruptors that did not make it into the work (Hirschfield, Hirschfield, and Flaws 1996; Lucier and Hook 1996).

By the end of 1996, it's clear that actors in different spheres took their positions and relatively little changed from 1991 to 1996. Social actors remained receptive for the entire five-year period, their focus on endocrine disruptors and proponents' point of view making the substances socially relevant and helping to spur political action. Regulatory actors were led by proponents to a particular conclusion, that of the need to regulate endocrine disruptors, through their work in social spheres and in Congressional hearings. Scientific actors responded to proponents' claims with questions, questions that proponents did not answer and largely ignored. That led to a spectrum of opinions within the scientific community, a spectrum that came to resemble a dichotomy more and more in the years following the regulation of endocrine disruptors.

The Food Quality Protection Act of 1996

Though scientific detractors of the endocrine disruptor concept continued to express doubt about its claims into 1996, those detractions did not halt regulatory action. In July of 1996, both House committees that held hearings in 1995—the House Agriculture Subcommittee on the Department of Operations, Nutrition, and Foreign Agriculture and the House Commerce Subcommittee on Health and Environment—released their final reports on the Food Quality Protection Act of 1996 (formerly of 1995).[17]

Both committee reports show the success proponents had with convincing policymakers of the dangers posed by endocrine disruptors. The first committee, while not recommending any changes to the Act for the regulation of endocrine disruptors, noted that the EPA should be screening chemicals for endocrine effects but that they already had the authority to do so and therefore did not need that authority granted in the Food Quality Protection Act (Committee on Agriculture 1996, 56). The second committee concluded rather differently, advocating for significant changes to the bill with regard to endocrine disrupting chemicals (Committee on Commerce 1996). First, the Committee suggested the codification of the EPA's ability to request information about endocrine effects when evaluating new pesticides. As the first Committee noted, that was not strictly necessary, but explicit codification may have caused the EPA to request and use the information more frequently.

[17] It is important to note that both committees offered many changes to the Food Quality Protection Act, but only those relevant to endocrine disruptors are detailed here.

But the second Committee took things further, recommending an "Estrogenic Substances Screening Program," whereby the EPA was required to develop "a screening program … to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect at the Administrator may designate" (Committee on Commerce 1996, 25). Though the program did not give the EPA more statutory power, it did issue a direct mandate that the EPA consider the issue of hormonally active substances and take action where deemed appropriate (Committee on Commerce 1996, 54). The Committee's recommendations, if accepted, constituted a big step for the endocrine disruptor concept, official recognition by the federal government of the role of endocrine disruptors in pesticide testing. By accepting the recommended changes, Congress would have recognized both claims of the concept, that endocrine disruptors exist and that they pose a threat to humans and wildlife, as well as the category of endocrine disruptors, even in the face of its ambiguity.

The Food Quality Protection Act of 1996 unanimously passed and was signed into law on 3 August 1996 (H.R. 1627 104th Cong.). When it was passed in 1996, the bill had 243 cosponsors (H.R. 1627 104th Cong.). The final version contained many of the changes suggested by the second committee, including the mandate for an estrogenic substances screening program (H.R. 1627 104th Cong.).[18] Three days later, President Bill

[18] With the passage of the Food Quality Protection Act, Congress further charged the EPA with establishing a single health standard for pesticides as well as further protecting infants and children, quickly approving safer pesticides, creating incentives for development of better farming techniques, and using new scientific data on safety to periodically re-evaluate pesticides in use.

Clinton signed the Safe Drinking Water Act Amendments of 1996 (H.R. 1627 104th Cong.). The Amendments also contained an estrogenic substances screening program, which referenced the program in the Food Quality Protection Act and extended the provisions to potential contaminants in drinking water (H.R. 1627 104th Cong.). Together, the Acts increased the responsibilities of the EPA generally, but also particularly with endocrine disruptors.

This was success for proponents of the endocrine disruptor concept. In the five years since they started their efforts, they achieved all three of their main goals. They increased public awareness of the threat of endocrine disruptors. They stimulated scientific investigation of endocrine disruptors and their effects. And they saw the passage of a mandated screening program for endocrine activity. However, as with their successes in social and scientific arenas, proponents' success in the regulatory arena took a slightly different form than they may have liked.

In the Food Quality Protection Act, Congress only required the establishment of an estrogenic substances screening program. They made no mention of the term "endocrine disruptor," and though they did allow for focus on other endocrine effects, the legislation is largely aimed at estrogenic effects. As detailed more fully in Chapter 6, that is a result of the studies proponents used to push for regulation and the emphasis in popular media on estrogenic chemicals. Throughout the early 1990s, proponents used studies linking hormonally active chemicals to breast cancer, sperm declines, and shrinking penises. Each of those effects can be characterized as feminizing, a result of too much estrogen in the body. Though proponents certainly tried to link them to endocrine

disruptors more broadly, the Acts final language makes it clear that a much stronger connection was made between estrogenic chemicals and negative effects.

That could have meant that endocrine disruptors as a category would not be regulated. However, just after the passage of the Food Quality Protection Act, the EPA established the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) to determine the best methods for evaluating pesticides for hormonal effects to be included in the mandated screening program (EDSTAC 1998). Notice that the EPA adopted the term "endocrine disruptor" to describe hormonally active pesticides though they were not required to by the Act. The inclusion of endocrine disruptors in the EPA screening program was due to the work of endocrine disruptor concept sympathizers within the Clinton administration. Both Carol Browner, Administrator of the EPA, and Goldman, now the Assistant Administrator of the Office for Prevention, Pesticides, and Toxic Substances, moved to incorporate endocrine disruptor screening into the EPA before passage of the Food Quality Protection Act, and after its passage, helped to ensure that endocrine disruptors remained the focus rather than estrogenic chemicals (Friedman 1992; EPA 1996d; EPA 1996e; EPA 1996f).

A Study that Could Impact Scientific Support

Browner and Goldman's acceptance of endocrine disruptors did not reflect broader scientific acceptance or consensus. In 1996, the endocrine disruptor concept and category remained divisive due to the same issues as in previous years: a fundamental lack of agreement as to what makes an endocrine disruptor and a strong disagreement as to whether endocrine disruptors truly posed a threat to human health and therefore needed

to be regulated. In 1991, when proponents initially constructed the concept and category, they had little evidence of endocrine disruptors impacting human health other than the flagship example of DES. By 1996, little more evidence had accumulated, and what had was scientifically contested, like Wolff's breast cancer study and Sharpe and Skakkebaek's sperm decline findings (Saidi et al. 1999; Olsen et al. 1995; Safe 1994; Safe 1995; Krieger et al. 1994).

Much scientific disagreement centered around the concern that humans are exposed to very low doses of endocrine disrupting chemicals and in traditional toxicology, the dose makes the poison. With many toxic substances, the more one is exposed to, the worse the effects, the dose-response curve following a linear pattern. In the case of endocrine disrupting chemicals, like PCBs and dioxin, humans are exposed to very low doses throughout their lives, meaning that effects should be quite small. That especially made sense to many given the lacking scientific evidence of negative effects in humans.

A study published in 1996 sought to address that issue. In June, John McLachlan and his colleagues at the Tulane-Xavier Center for Bioenvironmental Research published "Synergistic Activation of Estrogen Receptors with Combinations of Environmental Chemicals" in *Science* (Arnold et al. 1996). In the article, McLachlan and his team reported on experiments that showed that mixtures of weakly estrogenic substances (like most industrial and agricultural chemicals) were up to 1600 times more potent than the chemicals alone (Arnold et al. 1996). The finding was quite spectacular and addressed one of the major concerns many scientists had with the endocrine disruptor concept: that humans were exposed to such small quantities of such weak estrogens that endocrine

disrupting effects would be unlikely. McLachlan and his colleagues showed that it did not matter if humans were exposed to small quantities of weak estrogens, if they were exposed to mixtures of those estrogens as most humans are through their diet.

McLachlan's study seemed to be a starting point for building scientific consensus around endocrine disruptors, as it answered a large issue with the concept and category. Popular media widely published on the finding, writing nearly 150 articles on endocrine disruptors in 1996, showing their acceptance of the endocrine disruptor concept (Krimsky 2000). Following McLachlan's publication, several researchers set out to replicate his findings.

As that potential site for agreement underwent scientific examination, another publication showed the continued division between the scientific community's response to the endocrine disruptor concept, and everybody else's. The same year as increased popular publication on endocrine disruptors and the passage of the estrogenic screening program, Colborn and her two co-authors, Dianne Dumanoski and John Peterson Myers, published *Our Stolen Future* (Colborn, Dumanoski, and Myers 1997). The book, written as a sort of detective story for a public audience, laid out the endocrine disruptor concept and the evidence supporting it, using stories from the field, interviews with scientists, and a driving message of action. *Our Stolen Future* was distributed well before it was published and was reviewed by scientists and journalists alike. While journalists provided largely positive reviews in publications like *The Washington Post*, scientific reviews were much more critical, reflecting the continued disagreement over the endocrine disruptor concept (Lee 1996; Krimsky 2000).

1997–2018: Entrenched Dissensus and the Role of Social Actors

In the years after 1996, the original proponents, who saw the endocrine disruptor concept situated in scientific, social, and regulatory spheres, played a diminishing role. They achieved their goals, if not in the exact way they intended, and the world looked very different from 1997 on. Beginning in 1997, after the regulation of endocrine disruptors, the scientific community split over the endocrine disruptor concept, becoming hostile, polarized between two sides. That hostility began around the time that McLachlan was forced to retract his miraculous findings from 1996. As the scientific community moved through the end of the 1990s, their disagreements became entrenched in a process described more fully in Chapter 5. In 2018, they remain strong and have had impacts on regulations in the European Union.

The dissolution of the scientific community of endocrine disruptor researchers is perhaps reflective of the unique science policy path endocrine disruptors took in the 1990s. Proponents did not focus on the scientists, the way they did on the general public and policymakers, largely ignoring scientific disagreements in order to achieve their goals. Once endocrine disruptors were regulated, and victory declared, the scientific discussion of endocrine disruptors became very political. Many researchers took sides: either the regulation of endocrine disruptors was right or it was ludicrous. Proponents worked hard to make the endocrine disruptor concept scientific, social, and regulatory. They succeeded in that, but one consequence has been that scientific neutrality is difficult to maintain.

From a regulatory perspective, the endocrine disruptor concept has faded. After the establishment of the Endocrine Disruptor Screening Program and the subsequent

debates over what that would look like, the system has been operating as is. Though leadership within the program has set goals to update the testing requirements to reflect updated scientific data, the program, and the EPA more broadly, is facing potential budget cuts that would make such changes difficult and there are no longer activist-scientists working so dedicatedly to convince policymakers of the danger posed by endocrine disruptors (EPA 2011a; EPA 2011b; Erickson, Hogue, and Morrison 2017; Song 2017).

Perhaps the only place where proponents had long term success is the social sphere. Though awareness of the endocrine disruptor category as a whole has diminished, awareness of particular endocrine disruptors remains high and social actors continue to have an outsize role in societal response and treatment of those chemicals. That played out particularly in the case of bisphenol-A (BPA) during the early 2000s. The media machine proponents took advantage of to bring awareness to endocrine disruptors has kept worry over the chemicals alive, with odd tests of what chemicals a reader may have been exposed to and the dire effects as a result (Kristoff 2018).

The Retraction of the McLachlan Finding

Replication of McLachlan's findings proved to be impossible. By 1997, it became apparent that no other lab could replicate the increased potency of hormonally active chemicals in mixture found by the team at Tulane (Vogel 2012, 116). Following much scrutiny, McLachlan issued a retraction in 1997 (McLachlan 1997). The retraction received very little media coverage, a point emphasized by Diane Katz in an article in the *Wall Street Journal* where she claimed that, "the endocrine disruptor apocalypse has been

cancelled" and that poor journalism, paid off by the W. Alton Jones Foundation,[19] overhyped it to begin with (Katz 1997).

In that same copy of *The Wall Street Journal*, Safe wrote a scathing article about "Another Enviro-Scare Debunked"—the endocrine disruptor one (Safe 1997). In the article, Safe presented the evidence used to gain public support for what he called the endocrine disruptor hypothesis: the link to breast cancer, the decreased sperm counts, and the additive mixture effects. He then trotted out information discounting them all before ending with a musing about whether Congress would revoke the changes to the law in light of the new evidence (Safe 1997).

Safe's editorial did not go unanswered, with one researcher castigating Safe for using one finding to dismiss an entire theory while another poked fun that he "seems obsessed with sperm" (*WSJ* 1997). Safe's article and the responses to it are emblematic of a schism within the scientific community that grew ever wider in the years after 1996. In 1994, 1995, and 1996, the scientific community of endocrine disruptor researchers sat along a spectrum, with some seriously doubting the endocrine disruptor concept and some taking the concept as fact, but the majority seriously investigating the claims made by proponents in order to create more knowledge about endocrine disruptors (see Chapter 4). That began to change in 1997, with researchers being more clearly divided between the two polarized ends of the spectrum (see Chapter 5). The polarization only increased after that.

[19] Colborn and Myers worked for the W. Alton Jones Foundation.

Continuing Scientific Disagreement

The scientific dissension over the endocrine disruptor concept is evident in a 1999 report by the National Research Council. In 1999, the National Research Council, which had been asked to review endocrine disruptor science in 1995, released their report on "Hormonally Active Agents in the Environment" (NRC 1999). The report did not shy away from the scientific disagreement on endocrine disruptors, clearly walking through the points of contention and describing the tense atmosphere at their meetings to develop the report (NRC 1999).

As mentioned previously, the NRC highlighted that one difficultly with reaching scientific agreement on endocrine disruptors was the different interpretation of evidence. This is explored more fully in Chapter 4. The NRC report highlighted a second issue as well: the definition of endocrine disruptors. The Council, in their report, refused to use the term "endocrine disruptor," due to the ambiguity inherent in it (NRC 1999, 17). As noted in the report, "[t]he endocrine system can be disrupted in many ways that would lead almost every chemical with a disruptive effect on the organism to be classified as an endocrine disruptor" and that "[e]ven the term 'disrupt' is subject to differing interpretations" (NRC 1999, 17). Instead, the Council used the term "hormonally active agent," undermining a key component of the endocrine disruptor concept.

The NRC report lays bare a fundamental division in the scientific community over endocrine disruptors. While different interpretations of endocrine disruptor studies and evidence may well be an insurmountable divide, the inability to agree on even the basic definition of endocrine disruptors certainly is. As the 1990s progressed into the 2000s, the scientific schism over endocrine disruptors grew and part of that is due to both sides

talking past each other. When proponents talk about endocrine disruptors and their effects, the other side refuses to acknowledge endocrine disruptors as scientific objects. They disagree on whether the topic up for discussion should be a topic for discussion. Due to that, the scientific community on endocrine disruptors in 2018 is deeply divided

BPA and Public Fear

In the late 1990s and early 2000s, researchers, policymakers, and members of the public engaged in a conflict to determine the appropriate used of BPA. BPA is a widely-used plasticizer, used for making plastics clear and strong. Originally discovered in 1891 and investigated as an artificial estrogen,[20] it was rediscovered in the 1950s by researchers at Bayer and General Electric (Vogel 2009). By the 1990s, BPA was used in the majority of plastic consumer products, including water bottles and baby bottles (Vogel 2009).

In 1997, researchers reported on observed hormonally caused adverse effects in BPA exposed animals (vom Saal et al. 1997). Not only did the authors of the study, who included vom Saal, find endocrine disruptor effects from exposure to BPA, but they found those effects at very low doses of the chemical. The endocrine disrupting activity of BPA at low doses was landmark. As discussed previously, one of the key issues many scientists had with the endocrine disruptor concept was that humans are only exposed to

[20] It is ironic that, as of 2018, BPA is labeled as an endocrine disruptor given that it was originally investigated as estrogenic. After Russian chemist Alexander Dianin synthesized BPA in 1891, it languished until the 1930s, when Charles Dodds and his colleagues investigated its use as an artificial estrogen (Dodds et al. 1938). The irony is that in 2018 we recognize that BPA disrupts hormone processes when in the 1930s, that was its purpose. Dodds and his colleagues later synthesized DES as a much stronger artificial estrogen (Dodds et al. 1938).

low levels of the chemical and therefore would not be affected by their hormonal nature. Vom Saal's study addressed that, demonstrating that even those low levels could be dangerous.

Following the 1997 reports on the adverse health effects of BPA exposure, several other studies found similar outcomes (Nagel et al. 1997; Colerangle and Roy 1997; Steinmetz et al. 1997; Vogel 2012). Remaining proponents of the endocrine disruptor concept labeled BPA an endocrine disruptor, and one that worryingly had effects in very small doses. That finding, and in particular the work of activist-scientist vom Saal, spurred a large public campaign to desist the use of BPA, particularly in products used by infants and children, as they were at higher risk (Vogel 2012). While the public campaign was quite successful, a parallel regulatory campaign was less so.

The continually emerging evidence as to the dangers of BPA led to a number of proposed bills to limit its use, all of which failed (Vogel 2009). But continued public outcry prompted the FDA, in 2008, to convene a panel to reassess the safety of BPA, after reassuring consumers for years that the substance was safe (FDA 2018). The panel's findings were not novel, with members stating that more research was needed to draw any firm conclusions as to the toxicity of BPA (FDA 2018). But many supporters of the endocrine disruptor concept, including vom Saal, claimed that the evidence of BPA's toxicity was damning and that action was needed (vom Saal et al. 2007).

BPA and the drama that played out around it represents an interesting reversal in the endocrine disruptor story. For much of the 1990s, proponents found a receptive audience in policymakers eager to act on endocrine disruptors to protect children and reduce breast cancer diagnoses. Regulators were far less receptive to vom Saal and

others' arguments about BPA and the threat posed by the chemical, issuing reports that highlighted the divided nature of the scientific community working with endocrine disruptors. The reports came back to the same scientific issues of the previous decade: endocrine disruptor studies could be widely interpreted by different individuals and there was still little agreement on what counted as an endocrine disruptor and therefore what study would convince everyone that BPA posed a threat. BPA is one area where the division of the scientific community had an impact, one not in the proponents favor as regulators did not side with them.

Interestingly, in the case of BPA, it was social actors who played the biggest role in prompting action. Following the FDA panel report in 2008, the agency took no action. But in 2009, following boycotting by a large number of consumers, the use of BPA in baby bottles ceased after six producers decided to stop using it. That was action—curbing the use of a recognized endocrine disruptor—without the help of the FDA or EPA. Instead, the public and their buying habits were in the driver's seat. In the early history of the endocrine disruptor concept and category, public media played a key role, fully embracing proponents' ideas and selling them to a wide public audience. In the 1990s, mothers in grocery stores knew about endocrine disruptors because journalists were writing articles about them. The media propped up the largely empty concept and category in the early years.

By the 2000s, consumer groups and public fears took over that role. Vom Saal's findings about BPA were picked up by organizations like the Environmental Working Group, organizations that them told their members "BPA is a problem, it could be damaging your children" (Shannon 2008; Blake 2014a; Blake 2014b). Those members

then put pressure on manufacturers to reduce their use of BPA. The public propped up one endocrine disruptor, BPA, the same way popular media propped up the entire category in the 1990s.

Several states eventually banned the use of BPA in baby bottles, and in 2012, the FDA followed suit, though they maintained the safety of exposure to low levels of BPA (FDA 2018). As of 2018, it is common to see products adorned with large "BPA Free" labels as testament to the public's power. Unfortunately, most of the public neglected to ask what BPA was replaced with. The answer is usually bisphenol S (BPS), a substance that studies have shown may be significantly more toxic than BPA (Ahsan et al. 2018).

Conclusion

Between 1991 and 1996, endocrine disruptors followed a unique science policy trajectory. Proponents of the concept and category started with convincing social and regulatory audiences, growing support for what many in the scientific community criticized as flawed ideas. Ultimately, the scientific disagreement over the existence of endocrine disruptors and the threat they posed did not impact their regulation. Proponents saw success in their tactics to introduce endocrine disruptors a serious problem for human health and to push for their regulation. Those tactics were based on a small, but powerful group of effects and were aided by social trends and changes, like the shift away from the cancer paradigm.

In this chapter, I have followed the science policy trajectory of endocrine disruptors by pulling on two threads: how proponents pushed their concept and category in to scientific, social, and regulatory contexts and how actors in those contexts pushed

back. Proponents' tactics remained largely the same in all three arenas, where they focused on a narrow set of scientific studies to paint a threatening picture of endocrine disrupting chemicals. Through that, proponents gained the support of popular media, who accepted their ideas and wrote doomsday predictions of shrinking penises and the loss of masculinity as a result. Proponents worked more carefully in regulatory arenas, carefully managing the studies they used and the overall image they presented of endocrine disruptors. In doing so, they were able to tie endocrine disruptors to effects and diseases with social and political capital, thereby making endocrine disruptors something policymakers wanted to regulate. In the scientific arena, proponents put little effort and that saw the proliferation of opinions on the endocrine disruptor concept and what should be done about endocrine disruptors. As the 1990s progressed and proponents made progress in social and regulatory context, scientific disagreement increased, ultimately resulting in a polarized scientific field.

In the next three chapters, I write in more detail about the tactics proponents used and their consequences, referring back to much of the history covered in this chapter.

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CHAPTER 4

DISAGREEMENT DISSECTED, THE SPECTRUM OF AGREEMENT ABOUT THE ENDOCRINE DISRUPTOR CONCEPT IN THE 1990S

INTRODUCTION

The endocrine disruptor concept, as a scientific, social, and regulatory object, interacted extensively with each of those worlds throughout its life. In the last chapter, I showed how individuals in science, society, and regulation responded to the missing aspects of the concept. Proponents did not present a way to identify endocrine disrupting chemicals, delineate what counted as an endocrine disruptor, or describe mechanisms through which endocrine disruption might occur. Those lacks presented different problems in different areas. In the following three chapters, I will home in more closely on how scientific, social, and regulatory communities dealt with the multifaceted nature of the endocrine disruptor concept.

In this chapter, I will focus on how different individuals in the scientific community studying endocrine disruptors evaluated the concept. The endocrine disruptor concept is twofold: that endocrine disruptors exist as chemicals that disrupt hormone systems to negative effect, and that such chemicals pose a clear and immediate threat to human and wildlife populations. When proponents of the concept first presented it in 1991, they explicitly identified endocrine disruptors as scientific, social, and regulatory concerns. In doing so, they linked the scientific idea that chemicals disrupt hormone systems to the need to regulate those chemicals. It was not a case of scientific evidence first, regulatory and social response second, but all at the same time. As I will show in

this chapter, that meant that individuals weighing in on the concept did not only address the scientific legitimacy of the concept but also the regulatory necessity. Researchers conflated or linked their ideas about the scientific evidence supporting the existence of endocrine disruptors with the need (or not) to regulate them.

Throughout the 1990s, endocrine disruptor researchers evaluated the endocrine disruptor concept through their own research and in published opinion pieces in scientific and popular publications. In analyzing their evaluations, I have found that disagreements over the concept abounded. Often, arguments are presented as disagreements between two distinct sides. However, in the case of the endocrine disruptor concept, the disagreements are more accurately represented as a spectrum of viewpoints. Though researchers on either side of the spectrum held strong beliefs about the legitimacy of the concept, many more researchers along the spectrum took more measured views.

On one side were those researchers who originally drafted the idea, who viewed the existence of and threat posed by endocrine disruptors as proven fact. Those researchers relied largely on animal evidence to support such claims, as well as on the effects of the chemical diethylstilbestrol (DES) in humans. Researchers at that end of the spectrum included Theo Colborn and Frederick vom Saal, both of whom took their ideas about endocrine disruptors to the public and the government to demand action for what they saw as an urgent problem. Proponents of the endocrine disruptor concept very clearly indicated that because the scientific evidence for endocrine disruption was certain, regulatory action was obvious and should be immediate.

On the other end of the spectrum, different researchers argued that very little evidence supported what they called the endocrine disruptor hypothesis and that the

substances needed no new regulation. Individuals like Stephen Safe noted that animal data could not be extrapolated to humans given the lack of human evidence as a guide. Going even further, some detractors of the concept argued that evidence at the time indicated that endocrine disruptors were distinctly not a threat. They argued that the effects of the chemicals were balanced out by exposure to other chemicals, or that the chemicals did not push hormonal action outside the normal realm. Researchers holding that second extreme view were also vocal in public platforms, opposing the call for action due to scant justification. While detractors like Safe argued strongly against new regulations for endocrine disruptors, it is interesting to note that they did not decouple the scientific and regulatory aspects of the concept, instead following the proponents' suit that to evaluate the endocrine disruptor concept required an evaluation of scientific evidence and regulatory action.

Though researchers on either end of the spectrum dominated popular media coverage of endocrine disruptors, the researchers holding such strong views were in the minority. The middle of the spectrum, where the majority of endocrine disruptor researchers fell, was defined in terms of *mights* and *maybes*. Many researchers in the 1990s viewed what they called the endocrine disruptor hypothesis as still needing more evidence to establish its validity. Most agreed that animal evidence demonstrated that hormonally active chemicals could cause negative effects and that that demonstration necessitated further investigation into endocrine disruptors' potential effects on humans. Some advocated for the precautionary principle. Others argued that action could be warranted later but should not be taken yet. The middle group did not receive as much

attention and was not as ardent or active as the extreme groups, so it was easy to get the impression of a heated debate.

In this chapter, I detail the views held by individuals along the outlined spectrum above. I pay special attention to the evidence used by those individuals as well as their interpretation of the evidence. Through this, a couple of things become clear. First, that researchers in the 1990s were not simply weighing in on the scientific idea that substances may disrupt hormones. Instead, researchers evaluated the endocrine disruptor concept as it was presented in 1991—as a scientific, social, and regulatory problem. In that way, researchers frequently commented on both the scientific evidence for or against the concept as well as the impact of that evidence on whether the substances should be regulated. That is unique, in that discussions about scientific legitimacy and regulatory necessity occurred simultaneously, rather than one after the other. The simultaneous discussions are derivative of the activities of proponents to situate the concept in scientific, social, and regulatory contexts. The category of toxic substances called endocrine disruptors and its parameters was never decoupled from the endocrine disruptor concept as a whole, so a study of the substances was an evaluation of the concept.

Second, my analysis in this chapter highlights that researchers along the spectrum disagreed in their interpretation of evidence as well as their determination of what evidence should count in evaluating the concept. Though researchers on either end of the spectrum and through the middle often referenced the same studies and bodies of literature, they disagreed on the relevance of the studies to establishing endocrine disruption and what information the study provided regarding endocrine disruption. That

produced a wide range of views about evidence in the endocrine disruptor concept. Three researchers might interpret the same study in three different ways: as proof of endocrine disruption, as disproof of endocrine disruption, or as irrelevant to the topic of endocrine disruption altogether.

In that way, many researchers talked past each other on the topic of endocrine disruptors, something that was magnified by the popular media's coverage of the topic. As I discuss in the next chapter, that eventually led to strong polarization between endocrine disruptor researchers and the fading of the middle of the spectrum. That polarization still exists in 2018 and dominates attempts to regulate endocrine disruptors in the European Union (EU). This chapter will focus on the origins of disagreements that are being played out today: how individual researchers on the spectrum weighed evidence differently and called for very different kinds of action on the problem (or non-problem) of endocrine disruptors.

The Endocrine Disruptor Concept

The endocrine disruptor concept, as presented in the Wingspread consensus statement and later publications (Colborn, vom Saal, and Soto 1993; Colborn, Dumanoski, and Myers 1997), was comprised of two claims:

1. That certain chemicals can disrupt the hormone system to negative effect and that those chemicals are appropriately categorized as endocrine disruptors.
2. That endocrine disruptors pose a threat to the health of human and wildlife.

Those claims caught the attention of many in the 1990s. That attention resulted in a diversity of opinions that can most accurately be described as a spectrum, pictured below.

Individuals in the scientific community weighing in on the concept offered opinions on both claims, meaning that they discussed the scientific evidence supporting the idea that chemicals can disrupt hormone systems but also that those chemicals threaten the health of living organisms. Because the proponents who originally introduced the concept clearly linked the certain threat posed by endocrine disruptors to the need to immediately regulate them, the scientific aspect of the concept was connected to the social and regulatory aspect. That meant that scientists speaking about the concept frequently commented on whether endocrine disruptors should be regulated as a product of their certainty about the claims made in the endocrine disruptor concept.

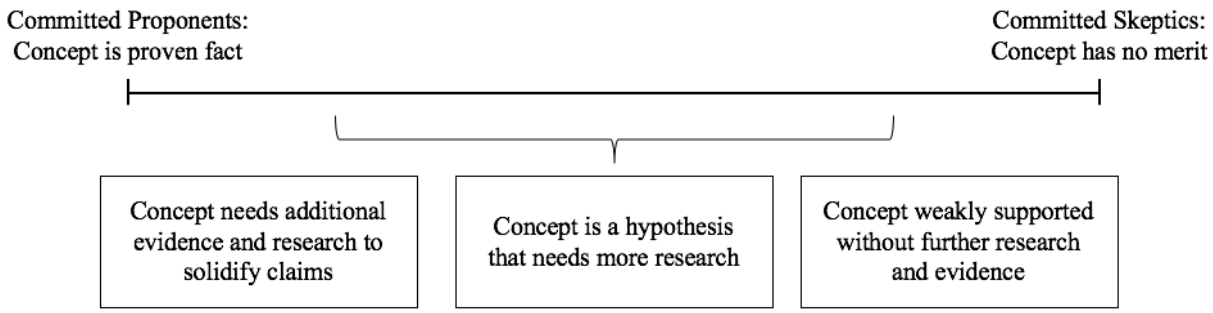

Figure 1. Spectrum of opinions on the endocrine disruptor concept

The scientists along the spectrum used three different bodies of evidence to support or oppose the claims made in the endocrine disruptor concept: laboratory evidence of the effects of different chemicals in animal models, wildlife evidence of the effects of chemical exposure in wildlife species, and human evidence of the effects chemicals have in different human populations. For proponents, all three bodies of evidence were relevant in supporting the endocrine disruptor concept and studies in each

clearly demonstrated the existence and danger of endocrine disruption. Skeptics, on the other, viewed all three bodies of evidence as problematic, both in terms of relevance to the question of endocrine disruption as well as whether the evidence demonstrated the existence and threat of endocrine disruptors. Researchers through the middle had varying view on the usefulness of laboratory, wildlife, and human evidence for substantiating the two claims of the endocrine disruptor concept. Throughout this chapter, I will show how researchers along the spectrum evaluated evidence for the endocrine disruptor concept and how they subsequently made claims about the need for regulation (or not).

One End of the Spectrum—Committed Proponents

On one end of the spectrum, the one that developed first historically, were those researchers who viewed the endocrine disruptor concept as proven fact. The individuals that populated the proponent end of the spectrum viewed evidence of endocrine disruptors as strong enough to support the endocrine disruptor concept entirely—meaning that for those researchers, endocrine disruptors posed a clear and imminent threat to the health of humans and wildlife. Laboratory, wildlife, and human evidence all undergirded the two claims of the concept and clearly showed the danger posed by endocrine disrupting chemicals. That threat necessitated action and researchers who saw endocrine disruptors as a threat pursued action, both publically and legislatively.

Proponents of the endocrine disruptor concept emerged early in the 1990s, immediately after the endocrine disruptor concept was proposed at the Wingspread meeting. Many proponents attended the Wingspread meeting in 1991, or worked closely with attendees (Colborn and Clement 1992; Colborn 1998b; Guillette 1998; vom Saal

1998). Committed proponents of the endocrine disruptor concept included Theo Colborn, who organized the Wingspread meeting, Frederick vom Saal, and Ana M. Soto. Remember that those researchers initially situated the concept as a scientific, social, and regulatory object and took actions throughout the 1990s to ensure that the concept was known and taken seriously by individuals in each of those worlds. In that way, it is not surprising that proponents of the concept argued that the legitimacy of the concept's claims clearly necessitated regulatory action. They made that position clear in their 1991 Wingspread consensus statement and pursued their goals of regulatory action and social awareness quickly thereafter, as shown in Chapters 2 and 3 (Colborn and Clement 1992; U.S. Congress Senate 1991, Testimony of Theo Colborn; Luoma 1992a; Luoma 1992b).

Three Bodies of Relevant and Certain Evidence

Beginning in 1991, proponents of the endocrine disruptor concept used three bodies of evidence to support the concept: studies of wildlife species exposed to industrial or agricultural chemical pollution, studies of laboratory animals and cell lines exposed to hormonally active chemicals (especially estrogen) at different stages of development, and any cases of human exposure to endocrine disruptors, especially the case of DES. According to proponents, each body of evidence clearly showed that endocrine disruptors existed and posed a public and ecological health risk.

The bulk of proponents' evidence as to the existence and harm of endocrine disruptors came from several decades of wildlife studies. Beginning in the 1950s, researchers throughout the US began to study wildlife species and their reaction to industrial and agricultural pollutants (Colborn, Dumanoski, and Myers 1997). Following

Rachel Carson's publication of *Silent Spring* in 1962, wildlife research expanded further (Carson 1962a; Griswold 2012). Proponents relied on wildlife studies to show that industrial and agricultural chemicals acted as endocrine disruptors and posed an ecological threat to wildlife species. They often pointed to identical wildlife studies to illustrate that point: Colborn's work with fish and bird species in the Great Lakes region, Louis Guillette's work with alligators in Lake Apopka, and Charles Broley's and others' work with bald eagles in the US and Canada (Colborn et al. 1990; Colborn 1991; Guillette et al. 1994; Broley 1958; Colborn, Dumanoski, and Myers 1997). Those works provided evidence that exposure to endocrine disrupting chemicals, in the form of industrial and agricultural pollution, resulted in developmental and reproductive setbacks. For proponents, those wildlife studies demonstrated that endocrine disruptors existed and harmed living organisms.

To illustrate the point more clearly, it is worth looking at a commonly used wildlife study more closely: Guillette's study of alligator populations in Lake Apopka, Florida. Guillette, a comparative endocrinologist at the University of Florida, Gainesville, began looking at the reproduction of the American alligator in the mid-1980s (Guillette 1998; Helbing, Tyler, and Iguchi 2015). Through that research, Guillette identified several reproductive and developmental abnormalities in alligator populations living in the highly-polluted Lake Apopka (Guillette et al. 1994). Those abnormalities included increased blood estrogen levels and large number of polynuclear oocytes in females and decreased blood testosterone levels and abnormally small phalli in males (Guillette et al. 1994). Guillette linked those effects with exposure to estrogenic chemicals present in the lake due to its proximity to an EPA Superfund site (Guillette et al. 1994).

Proponents used Guillette's study to support both parts of the endocrine disruptor concept. First, that endocrine disruptors exist as chemicals able to disrupt hormone systems to negative effect because in Lake Apopka endocrine disrupting contaminants did just that. And second, that endocrine disruptors posed a threat to wildlife populations, because the Lake Apopka alligator population suffered from decreased reproductive success as a result of exposure to endocrine disruptors. The other wildlife studies cited by proponents, which resembled Guillette's study in terms of methodology and findings, were used similarly (Colborn et al. 1990; Colborn 1991; Broley 1958; Colborn, vom Saal, and Soto 1993; Colborn, Dumanoski, and Myers 1997).

Endocrine disruptor concept proponents used a second body of evidence, laboratory studies, to solidify the claim that endocrine disruptors could disrupt hormone systems to negative effect, and therefore that they posed a threat not only to wildlife but also to humans. In the laboratory studies pointed to by proponents, researchers exposed laboratory animals or models to endocrine disruptors and observed the effects. Such studies included vom Saal's work with developing rats and estrogenic chemicals, Soto and Carlos Sonnenschein's work with estrogen contaminated laboratory equipment and a breast cancer cell line, and McLachlan's and others' decades of research on environmental estrogens (Colborn, Dumanoski, and Myers 1997; McLachlan 2016; Soto et al. 1991; vom Saal 1995; Colborn, vom Saal, and Soto 1993). Proponents used such studies to establish the causal link between exposure to endocrine disruptors and negative health effects in organisms.

As an example: proponents of the endocrine disruptors concept frequently used a story from Soto and Sonnenschein's laboratory to argue in favor of the concept. In 1989,

Sonnenschein and Soto received a delivery of new test tubes from Corning (Gross 2007; Colborn, Dumanoski, and Myers 1997). They were using the test tubes in an experiment to determine the role of estrogen in regulating cell proliferation (Colborn, Dumanoski, and Myers 1997). Upon using the newly delivered test tubes, Soto and Sonnenschein noticed that the breast cancer cells they were using (MCF_7 cells) proliferated in all their test tubes, regardless of the presence of estrogen—an anomalous result they had not seen before (Gross 2007; Colborn, Dumanoski, and Myers 1997; Soto et al. 1991). The two researchers discovered an estrogenic contaminant in the plastic test tubes, nonylphenol (Soto et al. 1991). They went on to discover several other estrogenic chemicals in commonly used plastic formulations (Cabaton et al. 2011; Markey et al. 2001; Schug et al. 2016).

Supporters of the concept cited the work of Soto and Sonnenschein as a clear demonstration that endocrine disruptors existed and could disrupt endocrine function, in that case by causing breast cancer cell proliferation (Soto et al. 1991; Colborn, Dumanoski, and Myers 1997; Schug et al. 2016). Further, because Soto and Sonnenschein had identified the endocrine disruptor as a component in a ubiquitous plastic, proponents argued that endocrine disruptors posed a threat to any humans or wildlife exposed to such plastic, which meant most of the human population and many wildlife species (Soto et al. 1991; Colborn, vom Saal, and Soto 1993; Colborn, Dumanoski, and Myers 1997; Schug et al. 2016). Other laboratory studies were used similarly, particularly as many in the 1990s focused on estrogenic chemicals in consumer products like food packaging (Schug et al. 2016; Vogel 2012).

Proponents heavily relied on both wildlife and laboratory studies to support both aspects of the endocrine disruptor concept: that endocrine disruptors existed and that they posed a public and ecological health risk. However, both sets of evidence only weakly supported endocrine disruptors as a threat to human health because neither wildlife nor laboratory studies connected exposure to endocrine disruptors with negative health outcomes in human beings. To more fully support that, proponents depended on a third body of evidence: human cases of exposure to endocrine disruptors. The human evidence that proponents used came in two forms, studies of the effects of DES and studies linking exposure to endocrine disruptors with developmental and reproductive anomalies.

In many ways, proponents depended on the case of DES to support the claim that endocrine disruptors threaten human health (Colborn, vom Saal, and Soto 1993; Colborn and Clement 1992; Colborn, Dumanoski, and Myers 1997). In the 1990s, DES was the only known instance where exposure to an endocrine disruptor had clearly and irrefutably been linked to negative human health outcomes (Herbst and Scully 1970; Abboud 2015). During the 1950s and 1960s, physicians prescribed DES, an artificial estrogen, to pregnant women at risk of miscarriage (Smith and Smith 1946; Smith 1948; Smith and Smith 1949; Langston 2010; McLachlan 2016). Starting in the 1970s, researchers found that men and women exposed to DES during gestation developed a number of rare cancers along with other reproductive abnormalities (Greenwald et al. 1971; Hill 1973; Henderson 1973; Giusti, Iwamoto, and Hatch 1995). Proponents frequently cited the case of DES to show that humans had been affected by endocrine disruptors before and therefore could be affected again, meaning that endocrine disruptors posed a threat to

human health (Colborn and Clement 1992; Colborn, vom Saal, and Soto 1993; Colborn, Dumanoski, and Myers 1997).

Proponents used the few other studies of endocrine disruptors and human health to corroborate that claim. In particular, researchers pointed to Joseph Jacobson and Sandra Jacobson's study on "Intellectual Impairment in Children Exposed to Polychlorinated Biphenyls *in Utero*," Nils E. Skakkebæk and Richard M. Sharpe's study connecting declining sperm counts and exposure to endocrine disruptors, and early studies indicating a potential link between endocrine disruptors and breast cancer (Sharpe 1993; Sharpe and Skakkebæk 1993; Jacobson and Jacobson 1996; Wolff et al. 1993; El-Bayoumy 1993; Davis et al. 1993). In each of those studies, researchers correlated some measure of endocrine disruptor exposure, most often levels of chemicals in the blood, with a negative health outcome. For example, in 1993, Mary Wolff and her research team reported that women with breast cancer had higher blood levels of organochlorines (Wolff et al. 1993). From that, Wolff and her co-authors suggested that those organochlorines may cause breast cancer (Wolff et al. 1993). Proponents of the endocrine disruptor concept used studies like Wolff's to support the claim that endocrine disruptors threatened the health of humans.[21]

[21] The three studies proponents most often cited to support the threat of endocrine disruptors in humans—the Jacobson's study of developmental impairment in children exposed to BPA, Skakkebæk and Sharpe's study of declining sperm counts as a result of increasing use of estrogenic chemicals, and Wolff's work connecting estrogenic chemicals to breast cancer—clearly picked up on social and political fears in the 1990s. As I show in Chapter 6, those three studies and their connection to social and political trends of the time allowed proponents to create a very specific and powerful narrative about endocrine disruptors and the need to regulate them.

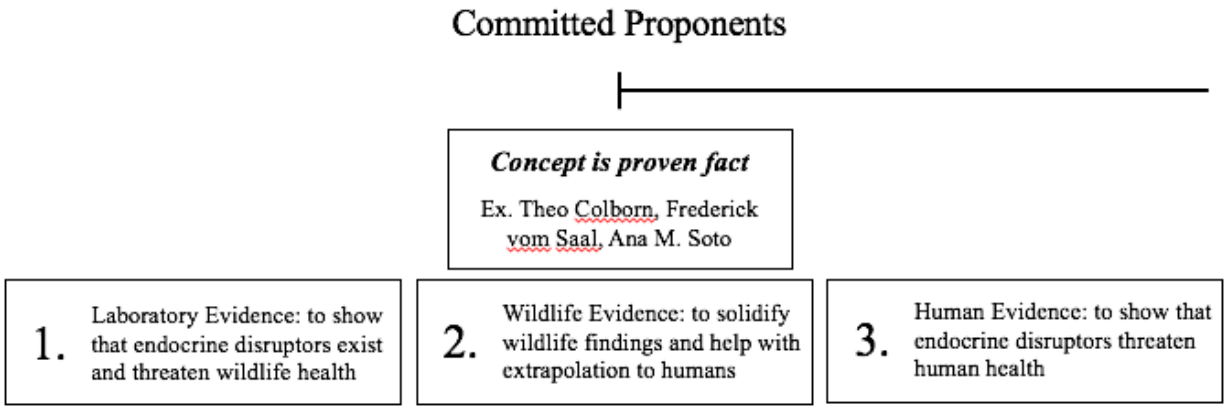

Figure 2. Proponents lines of evidence for their support of the endocrine disruptor concept.

Using three lines of evidence (wildlife, laboratory, and human), committed proponents of the endocrine disruptor concept supported both claims of the concept: that endocrine disruptors existed, and that they posed a threat to humans and wildlife. For proponents, the fully supported concept required action, action that would address the threat of endocrine disruptors by reducing exposure and increasing awareness (Colborn and Clement 1992; Colborn, vom Saal, and Soto 1993; U.S. Congress Senate 1991, Testimony of Theo Colborn). Proponents of the endocrine disruptor concept started calling for action in the Wingspread consensus statement, where they identified several needed regulatory changes and called for a public awareness campaign. To those ends, proponents of the endocrine disruptor concept frequently spoke about the human health threat posed by endocrine disruptors in media interviews and Congressional hearings (Luoma 1992a; Luoma 1992b; U.S. Congress Senate 1991; U.S. Congress House 1993; U.S. Congress House 1995a; U.S. Congress House 1995b).

Proponents of the endocrine disruptor concept, who viewed the concept as wholly supported, occupied one end of the spectrum on the validity of the concept. Using several

lines of research, proponents argued that endocrine disruptors existed and posed a threat to human and wildlife health. Individuals on the opposite side of the spectrum, presumably, had objections to the arguments made by proponents and the evidence they used.

The Other End—Committed Skeptics

Committed skeptics were on the opposite side of the spectrum from committed proponents of the endocrine disruptor concept. Skeptics emerged several years after proponents and doubted both parts of the endocrine disruptor concept proposed in 1991. For skeptics, the concept was unsubstantiated by available evidence, so much so that they unilaterally referred to the concept as a hypothesis. Individuals on the skeptics end of the spectrum interpreted the evidence used by committed proponents quite differently and also introduced other evidence that they claimed disproved the hypothesis, making it not only unsubstantiated but also invalid. Due to their opinion of what they called the endocrine disruptor hypothesis, committed skeptics argued against any regulatory action, following in the footsteps of proponents in their linkage of scientific certainty (or uncertainty) and regulatory necessity. Skeptics viewed the regulation of endocrine disruptors and the public anxiety around them as mistakes.

Following the meeting at Wingspread in 1991 and the conceptualization of the endocrine disruptor concept by the attendees, committed proponents began publicizing their claims. That publication largely took place in non-scientific spheres, rather in regulatory and public settings as discussed in Chapter 3. Just a month after Wingspread, one proponent, Theo Colborn, presented the concept at a Senate hearing on the regulation

of reproductive hazards (U.S. Congress Senate 1991, Testimony of Theo Colborn). And throughout 1992 and 1993, proponents gave many interviews with widely read newspapers, like *The New York Times*, broadcasting the endocrine disruptor concept and campaigning for regulatory action.

Skeptics began the debate over what they called the endocrine disruptor hypothesis only after it had been sensationalized by the media and begun to gain traction in the regulatory community, late in 1993 and into 1994 (Stone 1994; Safe 1994). The committed skeptic end of the spectrum, as with the other extreme, was not the most populous area on the gradient. But doubters of the endocrine disruptor concept, like Stephen Safe, Elizabeth Whelan, and Bruce Ames, vocally criticized the concept throughout the 1990s (Safe 1994; Safe 1995; Safe 1997; Kolata 1999; Whelan 1996; Stone 1994).

It is important to note here the nuance of skeptics' argument against the endocrine disruptor concept. Skeptics did not argue that chemicals could not interfere with normal hormone actions in the body. Researchers like Safe spent most of the 1980s studying just that, contributing to the field studying environmental estrogens (Andres et al. 1983; Bandiera et al. 1984; Biegel, Howie, and Safe 1989; Romkes and Safe 1988; Romkes, Piskorska-Pliszczynska, Safe 1987; Safe et al. 1989; Safe, Safe, and Mullin 1985; Yao and Safe 1989). Nor did skeptics argue that sometimes the effects of chemicals disrupting hormone function resulted in catastrophic effects. Safe and his colleagues did not dispute the hormonal nature of DES or that that hormonal nature caused negative effects in individuals exposed *in utero*. Instead, skeptics argued against the specific claims of the endocrine disruptor concept. First, that chemicals that interfere with endogenous

hormones are rightly called endocrine disruptors. Skeptics continued to research hormonally active chemicals in the 1990s, but refused to use the term endocrine disruptor over more accepted terms like environmental estrogen or hormonally active chemical (Safe 1994; Safe 1995).

Second, skeptics argued against the idea that agricultural and industrial chemicals that act hormonally posed any serious threat to the health of humans. Most, if not all, researchers studying hormonally active chemicals in the 1990s agreed that those chemicals could detrimentally impact the health of wildlife species like bald eagles, if those organisms were exposed to high doses through pollution or ecological accumulation (Vogel 2012; Schug et al. 2016). Skeptics took umbrage at the claim that those same chemicals threatened the health of humans not only because humans were exposed to such small doses of the chemicals but also because of the utter lack of human evidence demonstrating any effects (Safe 1994; Safe 1995; Stone 1994). Both of those strikes against the endocrine disruptor concept led skeptics to argue against any regulation targeted at endocrine disruptors and spoke out against the legislation passed in 1996.

Rebuttal of Proponent's Evidence and New Evidence

Committed skeptics marshalled two kinds of evidence against what they called the endocrine disruptor hypothesis. First, skeptics rebutted or criticized the evidence used by committed proponents. Skeptics argued that certain studies used by proponents were methodologically unsound or not applicable to general populations of humans. In other words, they argued the relevance of the evidence used by proponents in determining the

legitimacy of the endocrine disruptor concept and the regulation argued for by proponents. Second, skeptics presented new evidence, evidence that proponents did not use, that they argued disproved or greatly called in to question both claims made in the endocrine disruptor concept. They applied both kinds of evidence to both claims made by proponents, but most skeptics largely focused on pushing back against the claim that endocrine disruptors threatened human health (Safe 1994; Safe 1995; Stone 1994; Vogel 2012). Few disagreed that endocrine disruptors posed an ecological risk.

In their rebuttal of evidence used by proponents, skeptics focused on methodological problems with the cited studies as well as the lack of data with regards to the effects of endocrine disruptors in humans. Skeptics argued that the evidence proponents used to support the claim that endocrine disruptors were a public health risk was flawed, meaning the claim was unsupported and therefore questionable. Proponents relied on a small number of human studies, along with the significant case of DES, to show that endocrine disruptors threatened human health (Colborn and Clement 1992; Colborn, vom Saal, and Soto 1993; Colborn, Dumanoski, and Myers 1997). In particular, proponents frequently relied on studies linking exposure to endocrine disruptors with breast cancer and declining sperm counts (Colborn, vom Saal, and Soto 1993; Colborn, Dumanoski, and Myers 1997; U.S. Congress House 1993; U.S. Congress House 1995a; U.S. Congress House 1995b). Skeptics asserted that those studies that proponents relied on had not been substantiated by the scientific process. As they repeatedly highlighted, both the studies linking endocrine disruptors to breast cancer and to declining sperm counts were the subject of scientific critique (Wolff et al. 1993; Davis et al. 1993; Sharpe 1993; Sharpe and Skakkebæk 1993; Saidi et al. 1999; Olsen et al. 1995; Safe 1994; Safe

1995; Krieger et al. 1994). Other researchers had failed to reproduce the results and noted issues with the methodologies of the original studies (Olsen et al. 1995; Saidi et al. 1999; Safe 1994). Skeptics therefore saw the evidence proponents relied on as flawed, calling in to question their claims that endocrine disruptors threatened human health.

Beyond criticizing the evidence that proponents did use, skeptics also flagged the evidence that proponents did not use: large scale epidemiological data. In the 1990s, there were relatively few epidemiological studies showing the effects of endocrine disruptors. Of the ones that existed, two were highly criticized for replication problems, Wolff's study of women with breast cancer and Skakkebæk's study of declining sperm counts (Safe 1994; Olsen et al. 1995; Saidi et al. 1999). The remaining epidemiological studies were small in scope, with researchers looking at very particular populations exposed to abnormally high levels of chemicals, meaning that skeptics refused to generalize them to larger human populations (Safe 1994; Safe 1995). Skeptics argued that if endocrine disruptors were such a threat to humans, more studies would have found effects (Safe 1994; Safe 1995; Nohynek et al. 2013; Zoeller et al. 2014). For doubters of the endocrine disruptor concept, the lack of large scale epidemiological studies on endocrine disruptor effects in humans called into question proponents claims that endocrine disruptors posed a public health risk (Nohynek et al. 2013; Zoeller et al. 2014).

Skeptics rebutted proponents' evidence for the endocrine disruptor concept in order to show that the concept lacked the evidentiary support that proponents claimed it had. Skeptics used new evidence to show that what they called the endocrine disruptor hypothesis was invalid, meaning that evidence worked against it in significant ways. They used three new kinds of evidence to show that: evidence about the dose and potency

of hormonally active chemicals, evidence of humans' natural protections against estrogenic chemicals, and evidence of environmental protections against the potential action of hormonally active chemicals.

Individuals who doubted the endocrine disruptor concept employed evidence of the dose and potency of endocrine disruptors against both claims made by proponents: that endocrine disruptors existed as a class of chemicals capable of disrupting hormone systems, and that they threated human health. Proponents of the concept labeled chemicals like polychlorinated biphenyls (PCBs), dioxins, and many pesticides (like dichlorodiphenyltrichloroethane) as endocrine disruptors that could impact humans (Colborn and Clement 1992; Colborn, vom Saal, and Soto 1993; Vogel 2012). Skeptics noted, correctly, that many of those chemicals were only weakly estrogenic and were present in the environment at very low levels (Safe 1994; Safe 1995; Safe 1998). That meant that most organisms, and especially humans, were exposed to extremely low doses of the very weakly estrogenic so-called endocrine disruptors. Skeptics like Safe pointed out that such chemicals did not have the potency to cause change in organisms at the levels most were exposed to (Safe 1994; Safe 1995; Safe 1998). And further, some natural compounds that humans had been exposed to for generations were more hormonally active and had resulted in no discernible health effects (Stone 1994; Safe 1994; Safe 1995). Using that evidence, challengers of the concept argued that hormonally active chemicals did not pose a large ecological or public health risk.

They also questioned whether many of the chemicals that proponents labeled endocrine disruptors could in fact disrupt the hormone systems of living organisms to negative effect. Skeptics did not argue that hormonally active chemicals, like DES, could

not disrupt the human endocrine system and cause negative health outcomes. But for skeptics, DES, a chemical recognized as harmful to humans, differed in significant ways from the industrial and agricultural chemicals labeled endocrine disruptors by proponents. DES, a synthetic estrogen, is three times more potent that natural estrogen and was prescribed in the 1950s and 1960s in very large doses (Meyers 1983; Abboud 2015). For skeptics, that made DES an environmental estrogen, and estrogenic substance, and hormonally active chemical. Not an endocrine disruptor. Unlike DES, most industrial and agricultural chemicals are only very weakly estrogenic and humans are exposed to very low doses of the chemicals (Safe 1994; Safe 1995). Because of that, skeptics argued that the many consumer chemicals labeled endocrine disruptors by proponents were unlikely to threaten human health (Safe 1994; Safe 1995).

Skeptics deployed two other forms of new evidence to further dispute the claim that endocrine disruptors threatened human health. Skeptics noted that several phenomena may protect humans from the hormonal activities of endocrine disruptors. Researchers like Neil McLusky highlighted that primates respond to estrogen differently than other animals, attaching various conjugates to estrogens in the blood, inactivating them (Stone 1994). Because of that, some skeptics argued that the minor estrogenic activity of industrial and agricultural chemicals was neutralized in the human body, meaning that the chemicals could not disrupt hormone function (Stone 1994). For skeptics, that partially explained why hormonally active chemicals affected wildlife but did not threaten the health of humans, who use conjugates to inactivate circulating estrogens.

Safe, a vocal skeptic, proposed a second argument regarding humans' protections against endocrine disruptors: an acid-base argument (Safe 1994; Safe 1995; Stone 1994). Safe studied, among other things, anti-estrogens, chemicals that inhibit estrogenic effects in the body. He argued that humans were exposed to just as many anti-estrogenic chemicals as estrogenic chemicals in their daily lives (Safe 1994; Safe 1995). The effects of both kinds of substances cancelled each other out (Safe 1994; Safe 1995). The result, for Safe, was a net effect of zero and a non-threat in endocrine disruptors.

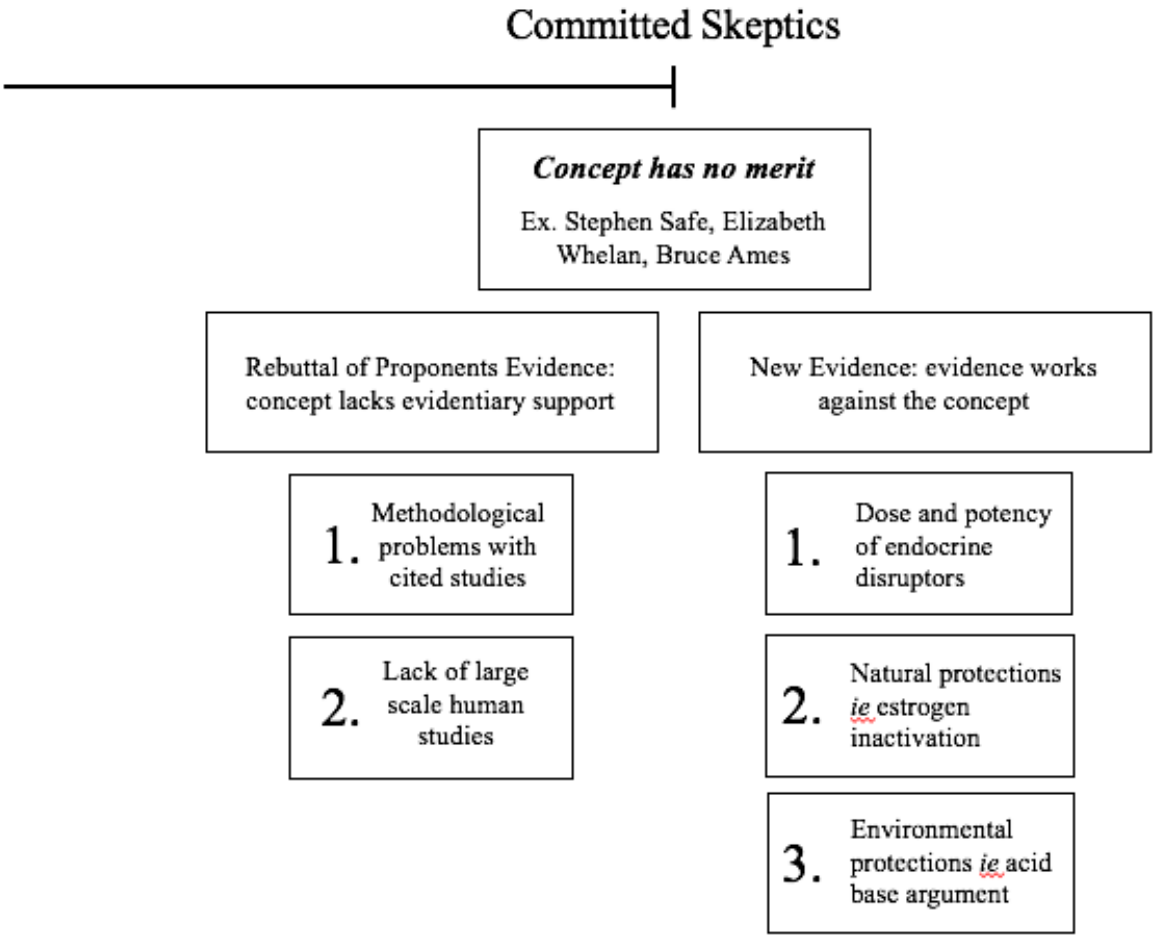

Figure 3. Skeptics lines of evidence for doubting the endocrine disruptor concept.

For skeptics, proponents' evidence failed to support the claims made for the endocrine disruptor concept, and new evidence actively worked against the claims. For those individuals, what they called the endocrine disruptor hypothesis was unsubstantiated and invalid, not worthy of further scientific consideration. Because of that, action taken on the basis of it was unjustifiable. Skeptical researchers spoke out against what they called the hysteria engendered by proponents of the concept, authoring editorials emphasizing the lack of evidence to fear endocrine disruptors (Safe 1994; Safe 1995; Stone 1994; Safe 1997). Whelan, in an interview for *The New York Times*, clearly articulated the main point for many skeptics: the endocrine disruptor hypothesis "ha[d] never been grounded in any reality" (Kolata 1999; Whelan 1996). Safe and other doubters also spoke out against the regulation of endocrine disruptors in 1996, calling for Congress to backtrack and remove the unwarranted regulations (Safe 1997).

Researchers on both extremes of the spectrum of the validity of the endocrine disruptor concept took strong stances on what the evidence surrounding endocrine disruptors showed and what should or should not be done on the basis of that evidence. Committed proponents and committed skeptics were vocal throughout the 1990s, playing out their disagreement in scientific, regulatory, and public spheres. But both ends of the spectrum were populated by a minority of endocrine disruptor researchers. Most researchers engaged in determining the validity of the endocrine disruptor concept resided somewhere in the middle of the spectrum.

BETWEEN THE TWO EXTREMES—THE MIDDLE OF THE SPECTRUM

The majority of endocrine disruptor researchers resided somewhere in the middle of the spectrum, meaning they saw the endocrine disruptor concept as having some validity but still requiring varying degrees more evidentiary support for the scientific certainty proponents claimed. Researchers in the middle viewed the evidence used by proponents as not fully substantiating the claims made in the endocrine disruptor concept. Like skeptics, they noted issues with the evidence for the endocrine disruptor concept. For that reason, middle of the spectrum researchers also referred to the concept as the endocrine disruptor hypothesis. But unlike skeptics, researchers in the middle of the spectrum acknowledged that endocrine disruptor studies indicated a need for further research to determine the existence or extent of endocrine disruptor effects in humans and wildlife. In keeping with that view, researchers in the middle of the spectrum called for more research on the concept rather than any regulatory decision making, conducting much of that research themselves.

Among those researchers in the middle, the variability of views is messy, meaning that the researchers did not organize themselves into well-defined groups with similar views. However, there were three views held by different individuals in the middle of the spectrum that help illuminate the spread among researchers. First, some of those researchers saw the concept as only weakly supported without the addition of further research. For those individuals, the hypothesis required more certain evidence to warrant further scientific consideration (Kavlock et al. 1996). A second viewpoint held that the concept was simply a hypothesis. Like any other scientific hypothesis, the endocrine disruptor hypothesis needed further evidence to substantiate it. For both those views,

researchers did not make regulatory considerations, firmly placing the concept in the scientific realm and no other. Finally, still others held that the endocrine disruptor concept required more evidence to solidify its particular claims, namely that endocrine disruptors threatened human health (Birnbaum 1994). But for those researchers, the claims had enough evidence to view them as likely validated and therefore some researchers began thinking about what regulatory action on endocrine disruptors might look like (Birnbaum 1994; Stone 1994). The differences among those three views may seem imprecise, mainly because the separation between researchers was not clear cut in the 1990s. However, those three views generally characterize many of the middle of the spectrum and played important roles in determining the fate of the concept.

Researchers holding those views emerged in the early 1990s, following the publication of the endocrine disruptor concept in 1991. Particularly outspoken middle of the spectrum researchers included Linda Birnbaum, John McLachlan, and Robert Kavlock (Birnbaum 1994; McLachlan 2016; Kavlock et al. 1996; Stone 1994). It is important to note that many researchers in the middle of the spectrum had been studying hormonally active chemicals for many years prior to the 1990s (McLachlan 2016; Vogel 2012). Though not explicitly investigating endocrine disruptors, as the term had not yet been coined, researchers in the middle of the spectrum were very familiar with the effects of chemicals labeled endocrine disruptors by proponents and had conducted many of the studies used by proponents to support their claims. Their familiarity with the study of endocrine disruptors, and endocrine disruptor precursors like environmental estrogens, shaped their view of the evidence used by proponents.

Regardless of their individual understanding of the validity of the endocrine disruptor concept, researchers in the middle of the spectrum interpreted the evidence used by proponents differently than proponents did. Like skeptics, researchers in the middle noted problems with the studies used by proponents. They also noted the lack of certain evidence to support the endocrine disruptor concept. For middle of the spectrum researchers, both problems impacted the validity of the concept as a whole, but particularly the claim the endocrine disruptors threatened human health.

In terms of problems with evidence, researchers in the middle identified some of the same problems as skeptics: the use of specific populations and the failure to replicate findings. Researchers in the middle commented on the fact that researchers had failed to replicate findings linking endocrine disruptors to breast cancer and declining sperm counts (Olsen et al. 1995; Saidi et al. 1999; Safe 1994). The failure to replicate findings also encompassed the fact that often two studies with similar experimental designs would produce differing results (Olsen et al. 1995; Saidi et al. 1999; Safe 1994). For example, between 1994 and 1995, three studies examined the effects of dosing female Sprague-Dawley rats with atrazine, a common ingredient in pesticides (Eldridge et al. 1994; Stevens et al. 1994; Connor et al. 1996). One study found that the atrazine resulted in decreased body weights and decreased levels of estradiol in the blood (Eldridge et al. 1994). However, a second study, with almost the same set up, found no change in weight (Connor et al. 1996). A third study found that atrazine administration caused breast tumors in younger rats, but had no effect on their weight (Stevens et al. 1994; Connor et al. 1996). Given scientific norms, such a morass of findings would indicate that some or all of the results were anomalies. However, because hormones and hormone-like

chemicals can affect many different endpoints, researchers in the middle struggled to determine how to make sense of inconsistent results.

Middle of the spectrum researchers also highlighted that particularly compelling wildlife studies, like Guillette's studies linking hormonal problems in alligators with pollution in Lake Apopka, were not generalizable (Stone 1994). The alligators Guillette studied were exposed to far higher doses of endocrine disruptors than most wildlife species would be, and therefore researchers could not assume that those findings would be common (Guillette et al. 1994; Stone 1994). For middle of the spectrum researchers, some of the evidence used by proponents suffered from large problems.

Further, researchers in the middle remarked on missing evidence that they argued was needed to fully support the claims of the endocrine disruptor concept (Kavlock et al. 1996; Birnbaum 1994). Like skeptics, they questioned why there were no large scale epidemiological studies to support the claim that endocrine disruptors threatened human health. But they also observed that proponents did not have the research to fully define, or characterize, endocrine disruptors (Kavlock et al. 1996; Birnbaum 1994). That observation goes back to what proponents presented in 1991. As discussed in Chapter 3, in many ways, the endocrine disruptor concept was empty, leaving many not knowing what counted as an endocrine disruptor, how to identify such substances, and how those substances might cause negative effects. Researchers in the middle saw three major questions about the qualities of endocrine disruptors:

1. What are the biological mechanisms of action for endocrine disruptors? How, biologically, does exposure to an endocrine disruptor result in an adverse health effect?

2. What was the dose response curve for endocrine disruptors? What dose of a particular endocrine disruptor resulted in a negative health effect?
3. What role does development play in the cause/effect relationship of endocrine disruptors and health effects? If an animal is at X developmental stage when exposure occurs, what kind of health effects can be expected?

Middle of the spectrum researchers highlighted that the qualities of endocrine disruptors were not yet clear, meaning that researchers did not yet have the capability to identify an endocrine disruptor from another kind of hormonally active chemical (Kavlock et al. 1996). That missing evidence, in the minds of researchers in the middle, left the endocrine disruptor concept still in question.

Where skeptics rejected the claims of proponents due to those problems, middle researchers viewed the claims as still open to question (Kavlock et al. 1996; Cooper and Kavlock 1997). More or less all researchers acknowledged that endocrine disruptors posed a threat to the health of wildlife. What many researchers grappled with was whether the substances threatened human health. Most recognized that the studies used by proponents demonstrated the potential that endocrine disruptors posed a threat to humans. Some argued that animal evidence could be an early warning system of sorts, indicating an underlying problem that may soon affect humans (Stone 1994). At the very least, researchers in the middle agreed that the studies used by proponents indicated the need to look more deeply into potential human health effects (Birnbaum 1994; Kavlock et al. 1996; Cooper and Kavlock 1997).

The conviction that there was a need to look more deeply at the effects of endocrine disruptors drove the action called for by researchers in the middle of the

spectrum. All called for and conducted more research on endocrine disruptors, while refusing to call for a particular kind of regulatory action. For many researchers in the middle of the spectrum, endocrine disruptors were not yet ready for regulatory consideration. Though proponents clearly set out to make the concept a scientific, regulatory, and social concern, researchers in the middle largely rejected that attempt. The research conducted by middle of the spectrum researchers can be seen as attempts to shore up, or lay to rest, the claims of the endocrine disruptor concept. Though not all researchers explicitly worked for or against the concept, the research they conducted largely addressed problems with the concept highlighted by skeptics and researchers in the middle.

Many researchers in the middle specifically tried to define the qualities of an endocrine disruptor.[22] McLachlan, who had studied environmental estrogens throughout the 1980s, conducted studies on the dose-response of particular estrogens (McLachlan 2016; Arnold et al. 1996; Toppari et al. 1996; Andersen et al. 1999). Others experimented with exposure at different doses at different developmental stages (Vogel 2012). Such

[22] During the 1990s, there was much debate over how to define endocrine disruptors. The term, according to some, was either not specific enough or too subjective. On the one hand, some researchers argued that the label of endocrine disruptor, as a chemical that disrupted the endocrine system, could be applied to nearly every chemical capable of affecting the body, given that they all likely affected the endocrine system in one way or another (NRC 1999). In that way, the term was too broad. Others argued that the terms "disruptor" and "disrupt" were subject to interpretation as far as what counted as relevant disruption (NRC 1999). Similarly, researchers argued over whether the definition of endocrine disruptors should include that the substances disrupt the endocrine system negatively or whether disruption, no matter how small, could be adverse and therefore the negative effect could be assumed (EDSTAC 1998).

researchers sought a clearer understanding of when an endocrine disruptor would be dangerous, something that is important in their regulation.

Other researchers in the middle of the spectrum conducted epidemiological studies on the effects of endocrine disrupting chemicals. In 1992, the Agency for Toxic Substances and Disease Registry began the Great Lakes Human Health Effects Research Program, "to characterize exposure to contaminants via consumption of Great Lakes fish, and investigate the potential for short- and long-term adverse health effects" (ATSDR 2014). Others conducted studies further investigating the link between breast cancer and endocrine disruptors, or examining the long-term health effects of exposure to endocrine disruptors *in utero* (Vogel 2012; vom Saal 1995; McLachlan 2016; Schug et al. 2016). Such studies addressed the claim the endocrine disruptors threaten human health, while also acting as the epidemiological studies that skeptics had called for.

Many researchers in the middle of the spectrum conducted research specifically aimed at finding a way to identify endocrine disruptors. Researchers like McLachlan and Kavlock developed screening assays to identify endocrine active chemicals and models to predict when hormonal activity might result in negative health outcomes (Bergeron, Crews, and McLachlan 1994; Andersen et al. 1999; Allen et al. 1994; Barnes et al. 1995). Kavlock spent much of the 1990s studying and designing ways to better study endocrine disruptors, helping to develop dose-response models and dosing standards (Barnes et al. 1995; Shuey et al. 1994). Other researchers endeavored to validate predictive assays and experimental techniques. Development of screening assays and predictive models by researchers in the middle of the spectrum demonstrates that some were thinking not only

about addressing scientific problems with the endocrine disruptor concept, but also about how to regulate endocrine disruptors should it be necessary.

The studies conducted by researchers in the middle of the spectrum stand in stark contrast to the strong actions called for by proponents and skeptics of the endocrine disruptor concept. Middle of the spectrum researchers stayed away from calling for regulatory action, instead calling for scientific action to address issues with the endocrine disruptor concept that would be key, should the substances ever be regulated.

But researchers in the middle of the spectrum were largely ignored in the 1990s. Media stories and Congressional hearings focused on the two extreme viewpoints, rarely talking to or quoting researchers in the middle of the spectrum (Luoma 1992a; Luoma 1992b; U.S. Congress Senate 1991; U.S. Congress House 1993; U.S. Congress House 1995a; U.S. Congress House 1995b). During the 1990s, two very small and very vocal sides of the spectrum played out their disagreements in scientific, public, and regulatory spheres, while the much larger but much quieter middle of the spectrum continued to conduct research meant to address issues of the endocrine disruptor concept working almost entirely in the scientific sphere.

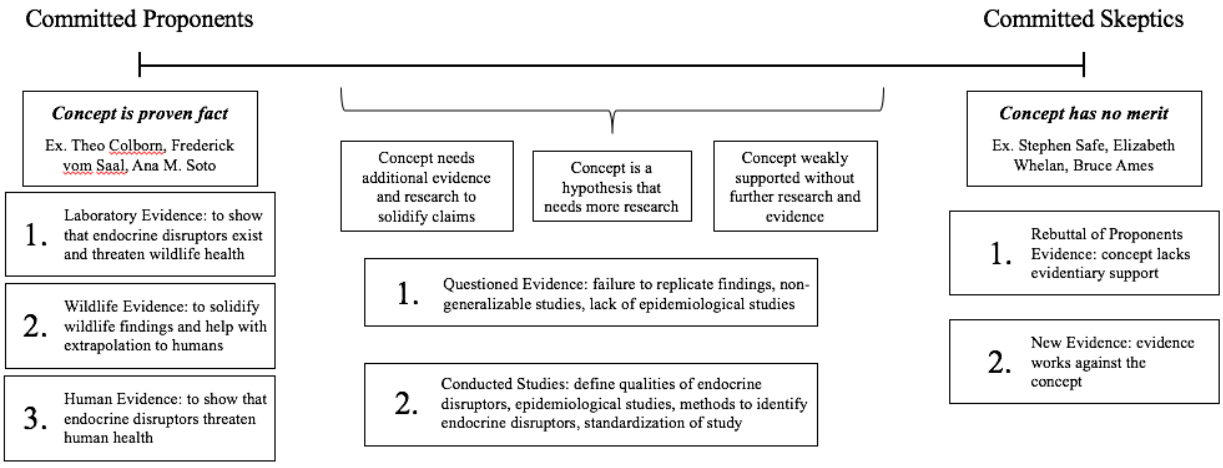

Figure 4. Spectrum of opinions on endocrine disruptor concept with accompanying lines of evidence.

The spectrum of views on the endocrine disruptor concept had real consequences in the 1990s and in 2018. The spectrum on the concept spanned two extremes and a great number of views in the middle. Individuals along the spectrum used many of the same lines of evidence to support very different views. The spectrum, and those lines of evidence, played out in the regulatory and scientific story of endocrine disruptors in the 1990s. Scientific, regulatory, and public discussions of the endocrine disruptor concept focused on the extreme viewpoints espoused by committed skeptics and committed proponents. Rarely were researchers in the middle paid much attention, though their research helped to further endocrine disruptor science. The result was an apparently polarized scientific field with proponents taking center stage in regulatory discussion.

The work of proponents led to the Endocrine Disruptor Screening Program, which is a deeply flawed piece of regulation. The testing it requires is expensive, time consuming, and largely fails to successfully identify endocrine disruptors. That cause of that is two-fold: the way in which the endocrine disruptor concept was situated by

proponents and the ignorance of middle views. The first has to do with the way the concept was introduced by proponents in 1991. As mentioned previously, that small group sought to place the concept in scientific, social, and regulatory contexts and worked consistently to bring awareness and action to each. However, as discussed in Chapter 3, the concept lacked a clear definition and explanation of what does and does not count as an endocrine disruptor. Individuals in different contexts handled the lack differently, as the spectrum of opinions demonstrates that individuals within the scientific community did as well. Proponents largely ignored flaws in the concept, in favor of strong social and regulatory action. Skeptics focused on the flaws, highlighting poor or missing evidence and arguing against regulation and social hysteria.

Researchers in the middle were the only group who sought to provide data in order to more clearly determine what makes an endocrine disruptor—doses when endocrine disruptors might be harmful, developmental stages when risk was high, what mechanisms an endocrine disruptor might act through. Researchers in the middle of the spectrum conducted studies to elucidate the qualities of an endocrine disruptor, qualities that are used to identify chemicals in regulatory settings. By passing regulation while ignoring the views held and work done by middle of the spectrum researchers, Congress left the Endocrine Disruptor Screening Program without the ability to identify endocrine disruptors, and therefore without the ability to successfully regulate them.

Those problems persist in the modern day. The Endocrine Disruptor Screening Program continues to struggle with how to identify endocrine disruptors when the scientific community cannot agree on a definition for endocrine disruptors. Those parameters that researchers in the middle tried to map out remain contested. Most

recently, that contestation has played out in the regulation of endocrine disruptors in the European Union, where the European Commission spent nine years attempting to come to an agreed definition of endocrine disruptors to direct regulation. As of 2018, a definition has still not been reached for many of the same reasons that researchers along the spectrum in the 1990s could not agree. Studies are interpreted widely, what counts as endocrine disruption is still not clear, and mechanisms of action are challenged.

The origins of disagreement in 2018 are laid out in this chapter. In the following chapter, I walk through how the middle of spectrum largely disappeared, leaving only the deeply polarized ends of the spectrum today.

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CHAPTER 5

HOW NON-SCIENTIFIC ACTORS AFFECTED THE SCIENTIFIC DISCUSSION OF ENDOCRINE DISRUPTORS

INTRODUCTION

This dissertation aims to examine how the endocrine disruptor concept appeared, got interpreted by different groups, and what role science played in the process. At the center of that question is the endocrine disruptor concept, which proponents set up as a scientific, social, and regulatory object in 1991. In Chapter 4, I showed how the tripartite nature of the concept drove scientists' evaluation of the endocrine disruptor concept as a whole, namely that scientists found themselves weighing in not only on the scientific legitimacy of the concept, but also on appropriate regulation. In this chapter, I will focus on another aspect scientific response to the social and regulatory nature of the concept. Specifically, how societal actors—industry, government, and media—affected the research conducted by those studying endocrine disruptors.

The study of endocrine disruptors and the evaluation of the endocrine disruptor concept encompasses almost three decades of research. The science started with the concept proposed in 1991 that included the claims that: 1. Endocrine disruptors exist as a category of toxic substances capable of disrupting endocrine systems and causing negative health outcomes; and 2. That such chemicals threaten the health of humans and wildlife. In the decades since that original statement, researchers involved in the field have looked at the qualities of endocrine disrupting chemicals (shared chemical makeups, similar effects, etc.) as well as how endocrine disruptors cause negative health outcomes

(mechanisms of action). Throughout that research, the endocrine disruptor concept remained an object of scientific, regulatory, and social concern, as the original proponents intended.

Due to that three-part focus of proponents, the scientific study of endocrine disruptors was never without social and regulatory interaction. Throughout the 1990s, popular media closely followed scientific progress, with newspaper articles, documentaries, and television interviews on the subject. Similarly, proponents directed regulatory focus toward endocrine disruptors almost immediately after proposing the concept in 1991, meaning that endocrine disruptors were never without questions of how to regulate them engaging policymakers and industry in the science. As I argue in this chapter, the involvement of those societal actors at key moments drove changes in the scientific study of endocrine disruptors, both in terms of what research was conducted as well as how the community of researchers interacted. I am interested in not only what endocrine disruptor researchers were studying, but also what the scientific community around endocrine disruptors looked like and how it changed over time.

The scientific study of endocrine disruptors breaks down into three eras. The first era, from 1991 to 1993, began with the introduction of the concept and ended with the engagement of popular media with the topic. The second era, spanning the three years between 1993 and 1996, began following the changes to the scientific community driven by popular media and ended with the entrance of more societal actors: industry and regulation. Industry and regulatory actors then drove toward the third era, which began in 1996 following the regulation of endocrine disruptors in the US and continues to the modern day. In this chapter, I walk through the three eras of scientific research and

discussion on endocrine disruptors. Within each era, I explain the main scientific focus, represented by a particularly vocal or influential researcher. Throughout the chapter, I emphasize how shifts in scientific discussion were often driven by social actors, especially the media and government. The eras of scientific research are as follows:

The first era, beginning in 1991 with the introduction of the endocrine disruptor concept, was dominated by discussions of a small group of researchers who spent much of their time inviting societal actors into scientific discussions. The presence of societal actors that could help proponents reach their goals of regulating endocrine disruptors and increasing public awareness of the danger posed by them dictated the actions of proponents during the first era, taking them out of the laboratory. Through media interviews and Congressional appearances, the small group focused on presenting the concept to non-scientific audiences, conducting relatively little scientific research. Therefore, the discussions among the endocrine disruptor scientists in the first era, scientific discussions of a kind, focused on how to increase regulatory and social attention on the concept. It was not that societal actors actively drove or engaged in scientific discussions in the first era, but rather that scientific discussions focused on how to engage those actors. During the era from 1991 to 1993, that group of researchers, represented by Theo Colborn in this chapter, spent time trying to gain social attention for the endocrine disruptor concept, which they hoped would lead to regulatory action.

The shift between the first era and the second era was precipitated by the engagement of a societal actor: the media. In 1993, several newspaper stories on the endocrine disruptor concept, in which Colborn figured prominently, took the fringe idea mainstream. That meant that the concept, which was not well known in the scientific

community, became a feature in larger society. With that social recognition, proponents of the concept reintroduced it in the scientific community. The result was increased scientific research.

The entrance of a much larger group of researchers into the field of endocrine disruptors marks the beginning of the second era in 1993, characterized by growth in the scientific community, increased funding for endocrine disruptor research, and deep scientific investigation of endocrine disruptors and their potential mechanisms. However, during the second era from 1993 to 1996, the media portrayed the scientific community as deeply divided and antagonistic, unable to agree. In truth, as discussed in Chapter 4, scientists in the second era held a wide variety of opinions on the endocrine disruptor concept and conducted intense and fruitful research with each other to investigate the different claims of the concept. The discrepancy between the polarized scientific community portrayed by the media and the actual scientific discussions occurring within that community is demonstrated by the relationship of Stephen Safe with Colborn. Both held opposing views on the endocrine disruptor concept, and the media portrayed them as enemies, when in reality they used their disagreements for productive investigation of hormonally active chemicals and their effects. Together, those two researchers represent two sides of the *apparently* polarized discussion.

That lack of true polarization changed in 1996, with Congressional action. When endocrine disruptors were formally regulated, the scientific discussion shifted dramatically. During the second era, researchers were united in trying to evaluate the concept as a scientific hypothesis, defining the characteristics of endocrine disruptors left undefined by the original proponents. But the regulation in 1996 triggered division in the

community in two ways. First, industry began to take a larger interest in endocrine disruptor science, funding studies and researchers that aligned with their goal of reducing regulatory burden. Second, many scientists engaged with the regulatory process that followed Congressional action, weighing in on how to regulate endocrine disruptors. Both of those resulted in the science being used in increasingly adversarial contexts, causing polarization.

Two strong and opposing sides reign in the third era of scientific discussion, which started in 1996 and continues in 2018. Those opposing sides, which began to form in the second era, consolidated after the appearance of industry and government on the endocrine disruptor landscape. One side, represented by Frederick vom Saal in this chapter, continued to promote the endocrine disruptor concept. The other side, with continued representation by Safe, rejected the concept entirely. In this section, I use the case of bisphenol A (BPA) and the debate over its safety in the early 2000s to portray the kinds of discussions that occur throughout the third era. I then explore the two debates that command the endocrine disruptor field in 2018: low dose responses and non-monotonic dose response curves.

In this chapter, I show that societal actors can have an outsize role on scientific discussion. In the case of the endocrine disruptor concept, societal actors like media and government took a science that was fringe, pushed it to mainstream, and then contributed to the fragmentation of the scientific community. That resulted in a field of study in which researchers largely cannot agree, something that has consequences for regulation into the modern day, most especially in contemporary debates in the European Union (EU).

REFRESHER ABOUT SCIENTIFIC IDEAS OF ENDOCRINE DISRUPTORS

Throughout this chapter I take advantage of some of the setup I did in Chapter 4, laying out the spectrum of opinions on the endocrine disruptor concept. The development of the spectrum, and its eventual destruction, followed the three scientific eras discussed in this chapter. Throughout, I refer to different ends of the spectrum as well as the views expressed by individuals along the spectrum. Given that, I have included the diagram from Chapter 4 to provide a brief overview.

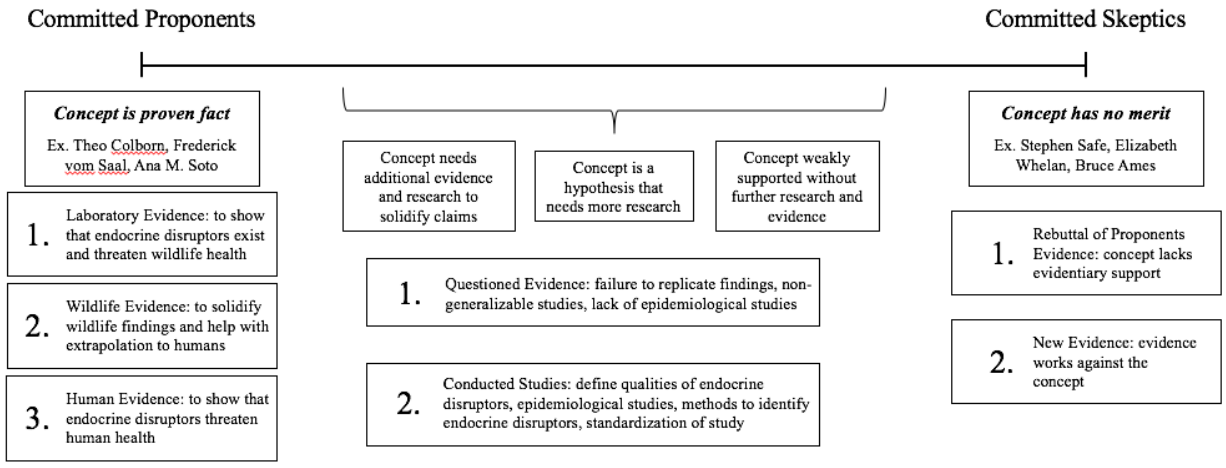

Figure 4. Spectrum of opinions on the endocrine disruptor concept with accompanying lines of evidence.

Throughout this chapter, I refer to each group—committed proponents, committed skeptics, researchers in the middle—and their respective beliefs. Because the spectrum largely played out during the second era of scientific discussion of endocrine disruptors, that section in this chapter is shorter, having large cross over with Chapter 4.

SCIENTIFIC ERA 1 (1991–1993): A SMALL GROUP WITH STRONG VIEWS

The scientific discussion around endocrine disruptors began in 1991, with the first introduction of the term at the Wingspread meeting on "Chemically Induced Alterations

in Sexual Development: The Wildlife-Human Connection" (Colborn and Clement 1992). Scientific discussion of hormonally active substances and their effects had begun much earlier, as discussed in Chapter 2, but 1991 marks the beginning of discussion specifically on endocrine disruptors.

The scientific community around endocrine disruptors during the first era was made up of a small group of researchers, well-known and respected in their fields, holding very strong beliefs about a fringe scientific idea: the endocrine disruptor concept. The group of researchers who discussed endocrine disruptors in the first era was small, a little over twenty individuals spread across diverse fields. Most of those researchers attended the Wingspread meeting in 1991, helping to formulate the endocrine disruptor concept, or worked in the labs of Wingspread attendees (Colborn and Clement 1992). The researchers almost across the board were respected in their fields: researchers like Howard Bern, an endocrinologist who laid out the effects of diethylstilbestrol, and John McLachlan, who as Scientific Director of the NIEHS had organized the environmental estrogen meetings of the previous decade. It is important to emphasize here that committed proponents of the endocrine disruptor concept, who engaged in endocrine disruptor discussion in the first era, were by no means fringe researchers. They were all well published in their respective fields. However, the researchers engaging with the science of endocrine disruptors in the first era did espouse strong support for and belief in a peripheral idea: the endocrine disruptor concept.

Their discussions about that concept largely did not occur in scientific forums. Between 1991 and 1993, there were few if any scientific publications on endocrine disruptors, other than the book authored by Theo Colborn and Coralie Clement laying out

the endocrine disruptor concept in 1992 (Colborn and Clement 1992). Otherwise, scientific actors engaged with endocrine disruptors between 1991 and 1993 spent their time inviting societal actors to acknowledge, and act on, the endocrine disruptor concept (Luoma 1992a; Luoma 1992b; U.S. Congress Senate 1991, Testimony of Theo Colborn; Colborn, Dumanoski, and Myers 1997). That can be seen in the testimony of Colborn and Ana M. Soto to Congress where they both introduced the endocrine disruptor concept and argued for regulation of endocrine disruptors, in the interviews Colborn, Soto, Earl Gray, and Michael Fry sat for with *The New York Times* and similar publications, and in the outreach to policymakers Wingspread attendees undertook outside of formal hearings (U.S. Congress Senate 1991, Testimony of Theo Colborn and Ana M. Soto; Luoma 1992a; Healy 1993; Vogel 2012).

Through that invitation of societal actors into the endocrine disruptor space, proponents of the concept shaped the way scientific discussions of endocrine disruptors played out through the 1990s. As emphasized elsewhere in this dissertation, proponents sought to situate the concept as scientific, social, and regulatory. Throughout much of the first era, proponents focus was on situating the concept thusly, hence the large emphasis they placed on social and regulatory discussions. In creating the three-part concept, though, the proponents coupled the scientific questions about endocrine disruptors with social and regulatory ones, meaning that during the second era, endocrine disruptor researchers across the spectrum were forced to weigh in on not only the science of the endocrine disruptor concept, but also whether and how endocrine disruptors should be regulated. This was explored in Chapter 4. Following the actions of proponents during

the first era, societal actors like media and government had a large role to play in scientific discussions about endocrine disruptors.

Few researchers epitomize that first era better than Theo Colborn. In 1991, Colborn brought together a diverse group of researchers at Wingspread to articulate the endocrine disruptor concept. She promoted that concept and what she saw as the political and social action demanded by the concept through the first era, from 1991 to 1993.

Scientific Spotlight: Theo Colborn

Theodora (Theo) Emily Colborn received her undergraduate education at Rutgers University in New Brunswick, New Jersey. After earning her degree in pharmacy, she married a fellow pharmacy student and together they operated a drugstore in New Jersey. In the early 1960s, Colborn and her husband sold their drugstore and moved to Colorado, where they opened another drugstore and raised sheep (and children) (Abboud 2014).

In 1978, at the age of fifty-one, Colborn returned to school at Western State College of Colorado in Gunnison, Colorado. There, she studied freshwater ecology and was appointed to the Colorado National Areas Program, a statewide conservation effort, by Colorado governor John D. Vanderhoof. Colborn graduated in 1981 and moved to Madison, Wisconsin, soon after, to pursue her doctoral degree (Abboud 2014).

At the University of Wisconsin, Madison, Colborn studied zoology, completing her dissertation on "The use of stonefly, *Pteronarcys californica,* Newport, as a measure of bioavailable cadmium in high altitude river system, Gunnison County, Colorado" (Abboud 2014). Following her graduation in 1985, Colborn was a Congressional fellow

in the Office of Technology Assessment in Washington, D.C., where she studied water quality and water quality assessment (Abboud 2014).

Colborn's work with water quality was her entry into the science of endocrine disruptors. In 1987, Colborn began a two-year project with the Conservation Foundation to examine the ecosystem of the Great Lakes area. Following that two year study, Colborn and her research team published *Great Lakes, Great Legacy?*, in which they laid out an analysis of the Great Lakes that showed that industrial and agricultural chemicals were poisoning the ecosystem (Colborn et al. 1990). Colborn and her colleagues' analysis showed that many of the wildlife species in the Great Lakes suffered from reproductive and developmental abnormalities because of chemical pollution (Colborn et al. 1990).

Following her work in the Great Lakes, Colborn began to formulate a hypothesis about chemicals with the ability to disrupt reproduction and development (Colborn 1998b). To determine whether her hypothesis had any merit, in 1991, Colborn organized a meeting at the Wingspread conference center with the help of John Peterson Myers of the W. Alton Jones Foundation. At that meeting, twenty-one researchers from diverse backgrounds all agreed on the merits of Colborn's hypothesis, coming together to formulate the endocrine disruptor concept.

Colborn saw the Wingspread meeting as changing the whole course and direction of her life (Colborn 1998b). As she described in a 1998 interview with PBS,

> Believe me, I didn't plan this. This is not what I had as a career goal or how I would spend my retirement years at all. This has just sort of happened, and people depend upon me. I can tell you there are a whole bunch of scientists out there who can explain this better, who know it better than I do. I feel compelled to do

> something to try to make change. And I guess that is why I went back to college in my old age. I wanted to get the education so that I could maybe undo some of the things that my generation basically foisted on society. (Colborn 1998b)

That quote very much encapsulates Colborn's outlook and personality. People who knew her described her as "a catalyst," "an empiricist," and "a fierce … advocate" (Safe 1998; Vogel 2012, 98–9). Whether Colborn intended or not, she became the voice of the endocrine disruptor concept in the first era, representing it at Congressional hearings and in media interviews. Throughout the rest of this section, the discussion of endocrine disruptors will be oriented around Colborn, as representative of the scientists and their actions in the first era.

A Fringe Scientific Discussion Inviting in Societal Actors

In 1991, the authors of the Wingspread consensus statement set the tone of the scientific discussion around endocrine disruptors by constructing the endocrine disruptor concept as scientific, social, and regulatory. In their statement, they outlined societal goals involving regulation and public awareness. Though the group identified several areas of needed scientific investigation, they largely focused on work outside of science: how to regulate endocrine disruptors and how to increase public awareness of the dangers posed by endocrine disruptors (Colborn and Clement 1992).

The Wingspread statement, as the first documentation of the scientific issues at play around endocrine disruptors, was distinctly not science-focused. The researchers instead placed emphasis on regulatory issues that the authors indicated could be partially addressed with scientific advancement, but that also required political and public buy in.

Essentially, the authors of the Wingspread consensus statement oriented the discussion of endocrine disruptors in the first era around social and regulatory changes rather than scientific investigation.

In doing so, proponents set the scientific agenda for the endocrine disruptor concept from 1991 to 1993. As the small group of researchers at Wingspread made up the entirety of the endocrine disruptor community in the first era, their focus on regulatory and social goals very much impacted the trajectory of the concept during its early years. Throughout those years, proponents focused on inviting social and regulatory actors into the scientific discussion of endocrine disruptors, through testimonies and interviews. Importantly, proponents presented the science of endocrine disruptors as certain, not inviting questions of what research is necessary but instead what regulatory and social action is necessary.

As an example of that: just weeks after Wingspread, Colborn spoke at the 1991 Senate hearing on "Government Regulation of Reproductive Hazards" (U.S. Congress Senate 1991). At that hearing, Colborn took the opportunity to restate the endocrine disruptor concept and argue for immediate action on endocrine disruptors (U.S. Congress Senate 1991, Testimony of Theo Colborn). The Senate hearing overall was about the implications of a recently published Government Accounting Office (GAO) report, which had found that reproductive hazards posed an increasing risk to humans and that the government was not doing enough to safeguard against them (U.S. Congress Senate 1991, Testimony of Eleanor Chelimsky).

In her written testimony for the hearing, Colborn submitted documentation of the issues and evidence discussed at Wingspread, drawing largely the same conclusions: that

endocrine disruptors posed a threat to humans and not enough was being done. She reiterated those conclusions and next steps in her oral testimony, laying out five actions points:

> First, it is imperative that the general lack of awareness of the presence of hormonally-active environmental chemicals be addressed, and the lack of awareness concerning the nature of loss of function which leads to loss of human potential and the concept of multi-generational exposure must be addressed as well.
>
> Two, the testing of products for regulatory purposes should be broadened to include hormonal activity, and these studies should be conducted over several generations, more than two generations.
>
> Three, because the impacts on wildlife and laboratory animals as a result of exposure to these contaminants are of such a profound and insidious nature, a major research initiative on humans must be undertaken.
>
> Four, banning of the production and use of many of these chemicals has not solved the exposure problem. These chemicals are still being released into the environment. New approaches are needed to prohibit release of these chemicals and new chemicals like them to reduce exposure.
>
> Five, it is urgent to move reproductive effects and functional loss to the forefront when evaluating health risks. Cancer and acute toxicity alone are not adequate to protect wildlife or human health. (U.S. Congress Senate 1991, Testimony of Theo Colborn)

Colborn called for regulatory change, public awareness, and a research initiative to determine the effects of exposure to endocrine disruptors in humans. Of the five goals she laid out, only the third one calls for a research initiative. All four other goals focus on increasing public awareness and modifying regulatory frameworks. Even in her call for a research initiative, Colborn did not mandate that the initiative attempt to determine *whether* there were effects in humans, but rather to determine what the effects were. Colborn's testimony follows the goals outlined in the Wingspread consensus statement and show that proponents seriously worked to establish the endocrine disruptor concept as scientific, social, and regulatory during the first era. The scientific community and discussion around endocrine disruptors from 1991 to 1993 was dominated by those attempts.

That becomes clearer through an examination of the popular media articles on endocrine disruptors in the first era (Luoma 1992a; Luoma 1992b; Healy 1993; Beil 1993; Peterson 1993). In 1992, Jon Luoma published two articles on hormonally active chemicals, one in *The New York Times* and the second in the *San Diego Union Tribune*. Respectively titled "New Effect of Pollutants: Hormone Mayhem" and "Cancer Not Only Contaminant of Concern," and both articles featured attendees from Wingspread drawing attention to what they saw as ineffective US regulation of endocrine active chemicals and the resulting public health crisis (Luoma 1992a; Luoma 1992b). Other popular news articles from the first era show the kind of science proponents used to support their claims about endocrine disruptors and generate social and regulatory attention. In articles like "Toxic Chemicals' Role in Breast Cancer Studied" and "Decreasing Sperm Counts Blamed on the Environment," the media picked up on the connection proponents drew

between endocrine disruptors and prominent diseases and effects like breast cancer and sperm declines (Beil 1993; Peterson 1993).

In particular, during the first era, proponents highlighted two scientific publications between 1991 and 1993: First, Ana Soto and Carlos Sonnenschein's work on how consumer plastics made with endocrine disrupting chemicals caused breast cancer cell lines to proliferate abnormally fast (Soto et al. 1991). Second, Nils E. Skakkebaek and Richard M. Sharpe's work linking estrogenic chemicals with declining sperm counts worldwide (Sharpe 1993; Sharpe and Skakkebæk 1993). Both articles contained science that pointed to disastrous outcomes for the public—breast cancer and low sperm counts—due to endocrine disruptors. Therefore, proponents of the endocrine disruptor concept used both articles heavily in their push to direct discussion toward social and political action (Luoma 1992a; Luoma 1992b; U.S. Congress Senate 1991, Testimony of Theo Colborn; Colborn, Dumanoski, and Myers 1997).

In that way, social and regulatory actors had a clear impact on the scientific discussion around endocrine disruptors not because they actively drove or participated in the scientific discussion, but because proponents oriented their actions and the science they used around gaining the attention of societal actors. Societal actors acted as magnets or lodestones that drew proponents' attention away from their scientific work and toward interaction with social and regulatory actors. In their attempts to gain the attention of such actors, proponents of the concept allowed societal actors like policymakers and public media to drive their work. Unlike in the second and third eras, where scientific discussion around endocrine disruptors changed as a result of actions taken by societal

actors, in the first era, scientific discussion around endocrine disruptors was changed in order to cause action by societal actors.

Scientific Shift 1 (1993): Media Attention and Scientific Visibility

The first shift in the scientific discussion of endocrine disruptors occurred in 1993, when two things happened: the endocrine disruptor concept received increased media attention and increased scientific visibility. Those two factors helped the endocrine disruptor discussion dominate a field. The concept went from fringe to mainstream.

The media attention on the endocrine disruptor concept popularized the concept and the risk posed by endocrine disrupting chemicals. In 1993, the concept was the subject of several popular news articles in sources like the *Los Angeles Times* and *USA Today* (Cone 1994a; Cone 1994b; Cone 1994c; Peterson 1993). Between 1993 and 1994, researchers linked endocrine disruptors with declining sperm counts, breast cancer, and shrinking alligator penises—three things almost guaranteed to catch the attention of the media (Sharpe and Skakkebæk 1993; Wolff et al. 1993; Davis et al. 1993; Guillette et al. 1994)). And they did (Begley and Glick 1994; Raloff 1995; Lutz 1996; Cone 1994a; Cone 1994b; Cone 1994c; Peterson 1993; Krimsky 2000).

In 1993, Skakkebæk and Sharpe connected estrogenic chemicals to declining sperm counts worldwide. Later that same year, a group of researchers published a piece titled, "Medical Hypothesis: Xenoestrogens as Preventable Causes of Breast Cancer," in *Environmental Health Perspectives* (Davis et al. 1993). In the article, the authors argue that the recent surge in breast cancer diagnoses might be attributable to increased exposure to environmental estrogens, citing as evidence several studies that found

elevated levels of estrogenic chemicals in the blood of women with breast cancer (Davis et al. 1993; Wolff et al. 1993). Those studies linked endocrine disruptors to another issue of public interest: breast cancer—the bogey man in the closet hunting mothers, sisters, wives.

A year later, in 1994, Louis Guillette and his colleagues published a study on "Developmental Abnormalities of the Gonad and Abnormal Sex Hormone Concentrations in Juvenile Alligators from Contaminated Control Lakes in Florida" (Guillette et al. 1994). Guillette and his co-authors provided evidence that, among other things, juvenile male alligators exposed to estrogenic environmental contaminants had abnormally small penises. As public media does, they latched on to the absurd and wrote a number of pieces on shrinking penises in alligators (Raloff 1995; Lutz 1996).

By 1994, endocrine disruptors had been linked to declining sperm counts in humans, breast cancer, and alligator penises. The studies were in no way conclusive, many only preliminary studies requiring significantly more investigation (Saidi et al. 1999; Olsen et al. 1995; Safe 1994; Safe 1995; Wolff 1995; Krieger et al. 1994; Safe 2000). And though media stories did acknowledge that uncertainty, they also used titles like, "Something is Attacking Male Fetus Sex Organs," and "Sperm counts down? Penises shriveled? Hey, Rush, don't blame it on feminists. It may be from chemical pollutants in water and food" (Goodman 1994; Begley and Glick 1994). All three linkages received large amounts of public attention. The media portrayed endocrine disruptors as the next catastrophe and proponents worked to help that perception (Luoma 1992a; Luoma 1992b; Raloff 1995; Lutz 1996). By the beginning of the second era,

endocrine disruptors were well known publically and people began calling for policymakers to do something about them.

At that point, in 1993, proponents reintroduced the endocrine disruptor concept to the scientific community. In 1993, Colborn, Frederick vom Saal, and Ana M. Soto published "Developmental Effects of Endocrine Disrupting Chemicals in Wildlife and Humans" in *Environmental Health Perspectives* (Colborn, vom Saal, and Soto 1993). The article was essentially a restatement of the Wingspread consensus statement. The authors presented evidence for the claim that endocrine disrupting chemicals pose a threat to humans and wildlife. In particular, they used DES as a clear, traceable model for endocrine disrupting effects in humans.

The publication of the endocrine disruptor concept in a well-read journal meant that the concept automatically drew increased scientific attention, given its increased visibility. Compounded with the work of public media, the endocrine disruptor concept was highly visible for scientific, social, and regulatory audiences. That helped the concept gain scientific traction. The transition between the first and second era demonstrates the success with which proponents situated the concept as scientific, social, and regulatory. By 1993, they got actors from all three areas to pay attention to the concept, gaining increased awareness, regulatory buy in, and growing scientific discussion.

The combination of the increased scientific visibility of the endocrine disruptor concept and the increased media attention pushed more researchers to enter the scientific discussion of endocrine disruptors. Between 1993 and 1994, the larger scientific community was almost forced to pay attention to the endocrine disruptor concept and

many came to realize that they disagreed with it, in part or entirely. The entrance of a societal actor—media—into the discussion of endocrine disruptors changed the scientific discussion, broadening it and also appearing to polarize it.

Scientific Era 2 (1993–1996): Apparent Polarization

The second era of scientific discussion about endocrine disruptors was dominated by an apparently polarized debate among scientists regarding the validity of the endocrine disruptor concept put forth by proponents in 1991. The second era saw the emergence of the spectrum discussed in Chapter 4. Following the intervention of popular media, many more researchers began engaging in the endocrine disruptor discussion, calling into question many of the assumptions made by proponents through the first era. Committed skeptics began the debate over endocrine disruptors in 1993, where before all researchers engaged with endocrine disruptors held largely the same views. But as was discussed in Chapter 4, the two vocal and polarized sides of the spectrum only appeared to command the scientific discussion from 1993 to 1996. That perception was emphasized by the continued role of popular media in the debate, who took advantage of the aggressive comments made by both committed proponents and committed skeptics about each other.

In reality, the second era of scientific discussion around endocrine disruptors was one of deep scientific investigation into the substances and their potential effects. Funding for endocrine disruptor research increased between 1993 and 1996, as the EPA, the W. Alton Jones Foundation, and others awarded millions in grants (Krimsky 2000, 24; EPA 1996a; EPA 1996b; EPA 1996c). Research on endocrine disruptors, especially

on areas left undefined by proponents—mechanisms of action, methods of detection, and long term health effects in humans—flourished. Several additional meetings were held at the Wingspread conference center and the EPA and NIEHS sponsored several work sessions on the endocrine disruptor concept and its impact (McLachlan and Korach 1995; Bantle et al. 1995; Kavlock et al. 1996; Barnett et al. 1996).

The second era was perhaps the era where the most scientific discussion actually took place between researchers with very different viewpoints on the validity of the endocrine disruptor concept. To demonstrate the discussion, and the many different views held on the concept, it is worth using Stephen Safe as a counter balance to Colborn in the previous section. Safe, throughout the second era, held directly opposing views to Colborn. Where she was a committed proponent, working throughout the 1990s to convince both scientists and non-scientists of the dangers posed by endocrine disruptors, Safe did just the opposite.

But while each had strong things to say regarding the other's scientific opinion, they also spoke well of each other. The relationship between Safe and Colborn is emblematic of broader scientific discussion during the second era, from 1993 to 1996, which occurred widely within the scientific community, while being portrayed as almost impossible by much of the media.

For that reason, I argue that the polarization of the scientific community during the second era was not as vehement as it was in the third era. Though many researchers had very strong things to say regarding the science of individuals on the spectrum, there was also a larger scientific push for further investigation, regardless of who was

investigating. That tension between the perceived polarization, which was extreme, and the actual polarization is typified by the relationship of Safe and Colborn.

Scientific Spotlight: Stephen Safe

Stephen Safe received much of his early education in Canada, before completing his doctoral degree at Oxford University in Oxford, England. Safe was trained as a chemist, and completed his doctoral dissertation on polyacetylenes in Dahlia, a genus of plants that includes the Boogie Woogie and the Star Sister.

Following a brief time spent at Harvard University in Cambridge, Massachusetts, Safe returned to Canada in 1968 to work as a research officer at the National Research Council of Canada in the Atlantic Regional Laboratory in Halifax, Nova Scotia (Safe 2013b). While working in Canada in the 1970s, Safe studied organochlorines, a group of chemicals that include DDT-like pesticides and polychlorinated biphenyls (PCBS). Safe described his first engagement with endocrine disruptors as taking place in the early 1970s, while he was working with Otto Hutzinger. Safe and Hutzinger studied the environmental breakdown of PCBs, finding that the substances are metabolized by several species (Safe 2013a; Safe 2013b).

During the 1980s, Safe began working at Texas A&M University in College Station, Texas. As a professor of veterinary physiology and pharmacology, Safe focused on tetrachlorodibenzoparadioxin (TCDD). TCDD is a polychlorinated dioxin and became the focus of scientific research in the 1980s after researchers had linked exposure to negative health effects in individuals exposed directly as well as their children (Abboud 2017; Schuck 1986; Committee to Review the Health Effects in Vietnam Veterans of

Exposure to Herbicides 1994). TCDD was a contaminant in Agent Orange, a pesticide used during the Vietnam War to clear dense vegetation as a part of Operation Ranch Hand (Abboud 2017; Schuck 1986). As a result, many scientists, including Safe, studied the toxicity and effects of TCDD. In particular, Safe looked at TCDD's effects on endocrine pathways, noting that TCDD behaves as an antiestrogen, blocking the action of estrogen in the body (Safe et al. 1985; Denomme et al. 1986; Keys, Piskorska-Pliszczynska, and Safe 1986; Safe et al. 1991; Safe 1999; Safe 2013b).

Into the 1990s, Safe continued to study the toxicity and effects of various chemicals, including those that act on endocrine pathways. He officially entered the scientific discussion of endocrine disruptors in 1994, in response to several publications linking breast cancer to environmental estrogens (Safe 2013a; Safe 2013b; Safe 1994). In an article addressing that linkage, Safe highlighted the implausibility of such an effect by pointing to the many compounds that act counter to environmental estrogens (antiestrogens) (Safe 1994; Safe 1995). Following that initial publication in 1994, Safe became the face of skeptics of the endocrine disruptor concept, frequently authoring editorials in both scientific and popular publications (Safe 1994; Stone 1994; Safe 1995; Safe 1997; Safe 2000; Safe 2013a; Safe 2013b).

But while Safe was a vocal and often antagonistic critic of the endocrine disruptor concept, he was and is a respected researcher within the field of toxicology (Safe n.d.). He is well published and has received several awards for his toxicological and environmental research (Safe n.d.). Safe also has a more whimsical side that gives insight into his character. In 2016, he gave a convocation address at Queen's University in Kingston, Ontario, his bachelors and masters alma mater. Safe wrote his entire address as

a poem, in which he emphasized the need to relish small victories and continue looking for opportunity (Armes 2016). He ended with the following verse:

My message to you who are graduating is to work hard and do your best.

Your studies and lessons learned at Queen's will help you pass the test.

Remember the past – wars, ethnic cleansing, any means to all ends.

Only you and your concern for others can help reverse these horrible trends.

It is up to you now, as the newest graduates of this fine institution.

Keeping up with advances in science and technology is only part of the solution.

Remember, if you fail to do so, your employer and coworkers will not lament,

and you will wind up living, again, in your parents' basement. (Armes 2016)

An Apparently Polarized Scientific Discussion

Throughout the second era of scientific discussion of endocrine disruptors, from 1993 to 1996, Safe and Colborn played starring roles, both publishing many scientific editorials on the concept and also writing or featuring in more popular stories in places like *The Wall Street Journal* or *The New York Times* (Luoma 1992a; Safe 1997). As noted previously, Colborn and Safe represent two ends of the spectrum of opinions on the endocrine disruptor concept. Their opinions received much media attention throughout the second era and it appeared as though the two greatly disliked each other.

However, Colborn and Safe spoke highly of one another. Colborn called Safe "one of the best scientists in the country," further arguing that endocrine disruptor proponents had been relying on his laboratory work for years (Colborn 1998b). To Colborn, Safe was funny, someone she laughed and had good times with. She fully

acknowledged the negative comments Safe made, certainly questioning his views, but she also claimed, "I am almost indebted to Steve Safe. The controversy is good for the issue" (Colborn 1998b). Safe, for his part, gave Colborn a Texas A&M nightshirt and portrayed her as the catalyst for the endocrine disruptor issue (Safe 1998). He saw both himself and Colborn as honest, both simply giving their opinions (different as they might be) on an important scientific issue.

Safe and Colborn's relationship sheds light on the scientific discussion of endocrine disruptors in the second era, from 1993 to 1996. Though their relationship appeared and was portrayed as hostile, the two viewed each other with respect, understanding that each offered a different opinion on science they both engaged with. Similarly, the scientific discussion of endocrine disruptors appeared polarized in the second era, but, in truth, it was a fruitful discussion filled with many different viewpoints (Safe 1995; Wolff 1995; see Chapter 4).

I laid out much of the scientific discussion in Chapter 4, with my detailing of the entire spectrum. I want to emphasize here that the majority of endocrine disruptor researchers resided in the middle of the spectrum and worked with varied other researchers to investigate the endocrine disruptor concept. Though individuals held strong viewpoints, often disagreeing with other individuals along the spectrum, much work on endocrine disruptors was conducted between 1993 and 1996. The second era of scientific discussion on endocrine disruptors was certainly fraught, but not aggressively polarized, as the media portrayed it. That changed in 1996 with the actions of more societal actors.

Scientific Shift 2 (1996): Regulatory Action and Industry

The period of apparent polarization ended in 1996, with the intervention of two societal actors: government and industry. While the second era of scientific discussion was characterized by researchers with a diversity of views, all of whom engaged each other on the scientific issues of the endocrine disruptor concept, the third era was dominated by truly polarized discussion. That shift was in part caused by regulatory action on endocrine disruptors and the entrance of industry in 1996, both of which caused the science of endocrine disruptors to be used in increasingly adversarial contexts.

In 1996, Colborn, John Peterson Myers, and Dianne Dumanoski published *Our Stolen Future* (Colborn, Dumanoski, and Myers 1997). In the book, written for a public audience, the authors lay out the endocrine disruptor concept and their supporting evidence. The authors start with a series of historical vignettes that they argue show the increasing reproductive and development problems of wildlife species exposed to industrial and agricultural endocrine disruptors. Each chapter of the rest of the book focuses on particular cases that demonstrate the widespread threat posed by endocrine disruptors and what work scientists have done to illuminate that threat. One chapter focuses on Colborn and her work in the Great Lakes leading to the Wingspread meeting, another showcases Frederick vom Saal's work on the role of hormones in development. The book ends with some ways that readers can reduce their exposure to endocrine disruptors in their own lives and a call for more regulatory and social action on the chemicals (Colborn, Dumanoski, and Myers 1997).

The book was widely read, with a foreword written by then-vice president Al Gore (Colborn, Dumanoski, and Myers 1997). It was translated into several languages

and reviewed in publications like *Science, Environmental Health Perspectives, Scientific American, Time,* and the *Washington Post* (Hirschfield, Hirschfield, and Flaws 1996; Lucier and Hook 1996; Kamrin 1996; Lemonick 1996; Lee 1996; Krimsky 2000). According to several chemical company representatives, *Our Stolen Future* unsettled the industry (Vogel 2012; Forsythe 1998).

The chemical industry had not been unaware of endocrine disruptors prior to 1996. In 1994, in response to committed proponents' work in DC to publicize the endocrine disruptor concept, Dow Chemical Company released a "Position on Endocrine Disruptors," in which they called in to question much of "Colborn's hypothesis" (Vogel 2012, 110). Within the document, Dow used many of the arguments of skeptics like Safe: that endocrine disruptors were only weakly estrogenic and therefore not dangerous, that natural estrogens found in plants had no apparent ill effects in humans, and that current regulations already protected against endocrine disruption (Vogel 2012).

However, the chemicals industry rarely spoke out against the endocrine disruptor concept until 1995, when it became clear that the public cared about endocrine disruptors and that some sort of regulation was likely (Vogel 2012; Krimsky 2000) In 1995, five industry groups created the Endocrine Issues Coalition: the Society of the Plastics Industry, the American Crop Protection Association, the Chemical Manufacturers Association, the American Petroleum Institute, and the American Forest and Paper Association (Krimsky 2000). The group set aside several million dollars to study the effects of hormonally active chemicals. That demonstrates industry taking notice of endocrine disruptors and the beginning of their public strategy for dealing with them. From 1996 on, the chemicals industry frequently issued statements regarding their

concern for the safety of chemicals, drawing attention to the money they spent testing their chemicals (Vogel 2012). A common refrain: because they care.

That public strategy continued after the publication of *Our Stolen Future* in 1996. As others have noted, the chemicals industry borrowed heavily from the tactics of the tobacco industry, adopting a united message of uncertainty regarding the endocrine disruptor concept (Vogel 2012). However, the chemicals industry did differ slightly in their tactics, largely staying away from personal attacks on endocrine disruptor scientists. As one representative commented, "… if they came out against Theo Colborn, nails out, fists blazing, that wouldn't fit in with their public image that they are trying to cultivate. If they say, "We care. We will look at this issue. We will study it," and then behind the scenes then try and defeat the amendments or then try and work with EPA to get their way, that works better" (Forsythe 1998). And work with (or against) the EPA they did.

The year 1996 saw the intervention of another societal actor as well: Congress through their legislation on endocrine disruptors. In 1996, Congress passed two pieces of legislation relevant to endocrine disruptors: The Food Quality Protection Act of 1996 and the Safe Drinking Water Act Amendments of 1996 (Pub. L. 104–170, 7 USC § 136 et seq.; Pub. L. 104–182 § 1316. Both mandated that the EPA establish

> [A] screening program, using appropriate validated test systems and other scientifically relevant information, to determine whether certain substances may have an effect in humans that is like an effect produced by a naturally occurring estrogen, or such other endocrine effect as the Administrator may designate. (Pub. L. 104–170, 7 USC § 136 et seq.)

That type of regulation was what committed proponents had been working toward since 1991. They therefore saw the legislation as a victory. Industry did not.

A month after the passage of the legislation, the EPA established the Endocrine Disruptor Screening and Testing Advisory Committee to make recommendations regarding the mandated screening program (EDSTAC 1998). The Committee included representatives from regulatory agencies, universities, environmental groups, and industry. The Committee met ten times between October 1996 and April 1998. Those meetings were far from congenial and contributed to the polarization of the endocrine disruptor field. In the Committee meetings, very different stakeholders were meant to come to some joint recommendations. Not surprisingly, proponents of the concept on the Committee, like Colborn, had vastly different recommendations than representatives from companies like Bayer Corporation. For Colborn, endocrine disruptors posed a serious and immediate public and ecological health threat. Without strong regulation, lives were endangered. For industry, testing or removal of potential endocrine disruptors represented hundreds of millions if not billions of dollars. Industry did not want strong, cumbersome endocrine disruptor regulations. Those two distinct goals in the context of a Committee meeting, meant that endocrine disruptor science was used adversarially—against the other side not to push toward better science, but to 'win.'

That competition played out with the definition of endocrine disruptor that would be used in the Endocrine Disruptor Screening Program. In short, industry representatives strongly advocated for a narrow definition of endocrine disruptors, one that included the causation of adverse effects (Vogel 2012). Such a definition reduced the likelihood that just because a chemical tested positive for hormonal activity, that it would be banned.

Proponents, on the other hand, argued that studies had shown that even minor endocrine activity, at the right point in development, could cause adverse effects. Therefore, the inclusion of causation of adverse health effects in the definition of endocrine disruptors was unnecessary.

A similar disagreement played out at the meetings of a National Academies of Science group, who had been tasked in 1995 by several agencies and Congress to evaluate the science of endocrine disruptors (NRC 1999). The group tasked with that evaluation met five times and had a similar makeup to the EPA Committee, meaning both industry and university scientists were represented.

Both the EPA Committee meetings and the National Academies meetings show the shift the scientific discussion of endocrine disruptors experienced between the second and third era. Researchers held increasingly polarized viewpoints argued in competitive contexts. The entrance of industry into the debate heightened that.

Scientific Era 3 (1996–): True Polarization

Throughout the third era of scientific discussion of endocrine disruptors, industry continued to play a role. Where the second era only appeared polarized, the third era, from 1996 on, truly was polarized. In the years after 1996, committed skeptics and committed proponents of the endocrine disruptor concept became further entrenched in their views, using a series of events between 1997 and 2000 to shore up their claims. Middle viewpoints largely disappeared. Industry continued their campaign to demonstrate care and consideration of the potential dangers of endocrine disruptors while also casting doubt on the endocrine disruptor concept as a whole.

By 2000, the third era was only a discussion, for lack of a better word, between two camps and that clearly played out in the case of bisphenol A (BPA). One individual set himself up against Stephen Safe, to represent proponents of the endocrine disruptor concept: Frederick vom Saal. Vom Saal was one of the leading scientists involved in the discussion of BPA in the early 2000s and his very unfriendly relationship with Safe helps to show the shifting tone in the scientific discussion of endocrine disruptors.

Scientific Spotlight: Frederick vom Saal

Frederick vom Saal completed his graduate education in the 1970s at Rutgers University in New Brunswick, New Jersey. He studied genetically identical strains of mice and the behavioral differences between those mice. In particular, vom Saal studied how the administration of different hormones during development could cause behavioral changes like pup-killing and aggression (Gandelman and vom Saal 1975; vom Saal, Gandelman, and Svare 1976; vom Saal, Svare, and Gandelman 1976).

Following his graduation from Rutgers in 1976, vom Saal continued that same research for much of the 1980s, engaging in discussions about environmental estrogens and their effects. During the 1980s, at both the University of Texas at Austin and the University of Missouri, vom Saal published on what he called the "womb effect." To vom Saal, the "womb effect" described how differing hormone levels *in utero* changed sexual behavior and reproductive development in mice (Vogel 2012, 125; vom Saal and Bronson 1980; vom Saal 1981).

By the 1990s, vom Saal had begun looking for the "womb effect" in mice exposed to synthetic estrogenic chemicals (Vogel 2012). While undertaking that research,

vom Saal was contacted by Colborn regarding the similarity between his lab findings and the wildlife effect noted by Colborn in the Great Lakes area. Upon hearing Colborn's early ideas about endocrine disruptors, vom Saal recalls saying, "[m]y god, this is astounding. I think you are onto something really important" (Mistreanu 2012). Vom Saal was an attendee at Wingspread and advocated for the endocrine disruptor concept throughout the 1990s and into 2018.

Like Safe, vom Saal was and is a respected experimentalist, well published and awarded within his field. Unlike Colborn, vom Saal does not have a congenial relationship with Safe (Safe 1998; vom Saal 1998; Hood 2005). Vom Saal, in the years after 1996, repeatedly attacked Safe due to Safe's receipt of industry funding for some of his research (vom Saal 1998; Safe 1998). Vom Saal's opinion of Safe and his funding is clear in statements like, "does it cause you to lie? And I am not suggesting that anybody is overtly lying. You don't need to do that in science. It is very easy for someone who understands the way a system works to set up an experiment to find exactly what you want to find" (vom Saal 1998). Vom Saal generally refuses to acknowledge differing opinions on the endocrine disruptor concept, going so far as to dismiss the opinions of Nobel Laureates due to the fast-moving pace of endocrine disruptor science (vom Saal 1998; Hood 2005).

Safe, for his part, openly admits that he and vom Saal are not friends (Safe 1998). He has called vom Saal's attack a "McCarthy-like tactic" and "an outright lie," while pointing to some of vom Saal's colleagues who have also received industry funding (Safe 1998). It would be easy to view Safe as simply an industry dupe, used like Clarence Cook Little by the tobacco industry, but endocrine disruptor science is more complicated. First,

Safe is as respected as vom Saal, each talented a experimentalist who has been conducting research on hormonally active chemicals for decades. Second, Safe's opinion is by no means fringe (Vandenberg et al. 2009; Vandenberg et al. 2012; Zoeller et al. 2014; Nohynek 2013; Lamb et al. 2014; Rhomberg and Goodman 2012). Endocrine disruptor science—the cause and effect of endocrine disruptors—is far less certain than the connection between smoking and lung cancer. Even in 2018, debate continues and neither side is without scientific merit.

Discussion of BPA as a Way to Conceptualize a Truly Polarized Field

The relationship between vom Saal and Safe is indicative of the larger scientific discussion of endocrine disruptors in the third era beginning in 1996. Discussion became antagonistic, publications filled with small jabs and dismissals, arguments becoming more heated. That is especially clear in the conversation around bisphenol A (BPA) in the late 1990s and early 2000s (Sharpe 2010; Ashby, Tinwell, Haseman 1999; Cagen et al. 1999; Vogel 2012; Sheehan and vom Saal 1997; vom Saal and Sheehan 1998; Lamb 1997; Fagin 2012). BPA is a widely-used plasticizer, used to make plastic clear and tough. BPA was originally synthesized in the late nineteenth century, and then investigated as a synthetic estrogen in the 1930s (Dodds et al. 1938). After the development of DES as a much more potent synthetic estrogen, BPA was largely forgotten until the 1950s, when it was rediscovered by chemists at Bayer and General Electric (Vogel 2009). Since 1957, BPA has been a major industrial chemical. By the 1980s, the chemicals industry produced one million tons of BPA worldwide, and in 2018,

production is over eight billion pounds (EPA 2010; CDC 2016). BPA production worldwide is a fifteen to twenty-billion-dollar industry.

Use of BPA in ubiquitous consumer products like food cans and plastic bottles went unnoticed until 1997. In 1997, vom Saal and his lab published a study on the effects of *in utero* exposure to DES and BPA on male reproduction in mice (vom Saal et al. 1997b). As vom Saal and his co-authors lay out in their 1997 article, researchers had proposed that estrogen played a role in prostate development just as androgen does (vom Saal et al. 1997b). Based on some previous research, vom Saal's lab attempted to determine the effect of *in utero* exposure to two synthetic estrogens on prostate development in mice. They found that administration of synthetic estrogens in very low doses resulted in prostate enlargement while high doses resulted in stunted prostate growth (vom Saal et al. 1997b).

From their data, vom Saal and his colleagues proposed that synthetic estrogens like BPA follow an inverted U dose response curve. Traditional toxicology assumes that dose response curves are linear: the more of a poison an individual is exposed to, the worse the effects of that poison. Though poisons had been shown to violate that assumption by the 1990s, most notably x-ray radiation, researchers still assumed that most substances followed a linear dose response curve (Fagin 2012). In 1997 and in follow up publications in 1998, vom Saal and his colleagues raised the possibility that BPA and other synthetic estrogens followed non-monotonic (non-linear) dose response curves (vom Saal et al. 1997b; vom Saal and Sheehan 1998). That meant that BPA and other endocrine disruptors could disrupt normal function at very low doses—parts per trillion, or a hundred-million-fold less than normal blood estrogen levels (Vogel 2012).

Vom Saal's findings were hugely impactful in 1997 because of their implications. For much of the 1990s, some researchers argued that endocrine disruptors did not threaten human health because humans are exposed to such low doses of endocrine disruptors in their daily lives (Stone 1994; Safe 1995; Safe 2000; Fagin 2012). But vom Saal's study showed that low doses, those encountered in daily life, could impact health if exposure occurred at certain points. That gave credence to the endocrine disruptor concept and the threat endocrine disruptors posed to human health.

It also threw a wrench in the regulatory testing of endocrine disruptors. To determine the toxicity of chemicals, toxicologists usually seek to find the no observed adverse effect level (NOAEL) and/or the lowest observed adverse effect level (LOAEL). The NOAEL is the highest level of exposure the results in no adverse effects. In other words, the NOAEL is a conservative value under which it is assumed that the chemical is safe. Many regulations of toxic chemicals take as their starting point the NOAEL. Once a chemical NOAEL is established, a regulatory agency may then decrease the value by one order of magnitude and make that smaller amount the amount of the chemical that is legally allowed to appear in a food product (Lagarde, 2015).

The potential toxicity of endocrine disruptors at very low doses identified by vom Saal reduced the value of NOAELs as a starting point. In light of vom Saal's findings, BPA's safe minimum dose may be zero, which would require its complete ban. Zero tolerance for trace levels of chemicals is very hard to enforce and also to achieve, if the particular chemical is in any way used in the production process. Given the wide use of BPA, that could be catastrophic. Further, because BPA and other endocrine disruptors

may follow a non-linear dose response curve, testing would require examination of far more doses than usual, making testing more expensive and time consuming.

Given the implications of vom Saal's findings for industry and regulation, a large controversy developed (Vogel 2012; Fagin 2012). First, according to vom Saal, he was approached by a representative of Dow Chemical Company. The representative stated the company's distress at vom Saal's findings and proceeded to dispute vom Saal's data (Shannon 2008). Vom Saal and his colleague, Wade Welshons, interpreted the representative's words as an unsubtle threat. Second, Colborn, as a member of the EPA Committee determining recommendations for endocrine disruptor testing, raised vom Saal's research to argue for the need for low dose testing and testing at different developmental stages. Industry representatives again disputed vom Saal's findings, pointing to the lack of replication. As Sarah Vogel put it, industry dismissed vom Saal's work as a "misguided attempt to hold up a flawed theory of endocrine disruption" (Vogel 2012).

In order to demonstrate the erroneous conclusions of vom Saal's study, industry (the Society of the Plastics Industry and the European Chemical Industry Council) funded John Ashby at AstraZeneca to replicate vom Saal's work (Vogel 2012). Vom Saal's lab played an active role in the replication, teaching Ashby's team their methods. Ashby's study found no statistically significant effects from the low dose BPA administration (Ashby, Tinwell, Haseman 1999). Neither did a second group's study, funded by Shell Chemical, Dow Chemical, General Electric, and Bayer (Cagen et al. 1999; Vogel 2012). Industry, and skeptics of the endocrine disruptor concept, framed both studies as putting to rest vom Saal's claims and definitively disproving the idea that low doses of endocrine

disrupting chemicals could have any effect. Following that message by industry, vom Saal and his colleague Danial Sheehan exchanged a set of essays with James Lamb, who worked for the private consulting firm Jellinek, Schwartz, and Connolly Inc (Sheehan and vom Saal 1997; vom Saal and Sheehan 1998; Lamb 1997; Vogel 2012). In those essays, neither side could agree on what was at issue. Vom Saal and Sheehan highlighted the need to reevaluate regulatory testing to account for low dose and non-monotonic dose response curves (Sheehan and vom Saal 1997). Lamb disputed the existence of such curves, explaining them away and sidestepping the issue of regulatory change (Lamb 1997). That conversation between vom Saal and Lamb demonstrates proponents continued efforts to make endocrine disruptors the subject of regulatory and social concern and to frame endocrine disruptors as a unique problem, something to worry about.

Given that viewpoint, vom Saal and other proponents pushed the FDA to reevaluate the safety of BPA (vom Saal et al. 2007). The FDA refused (Vogel 2009; Fagin 2012). The EPA, however, did consider low dose response and its implications (NTP 2000). The EPA asked the National Toxicology Program to review low dose literature and make recommendations (NTP 2000). The National Toxicology Program report, published in 2000, struck a moderate note, stating that:

> Low-dose effects, as defined for this review, were demonstrated in laboratory animals exposed to certain endocrine active agents. The effects are dependent on the compound studied and the endpoint measured. In some cases where low-dose effects have been reported, the findings have not been replicated. The

toxicological significance of many of these effects has not been determined. (NTP 2000, vii)

Not a ringing endorsement, but the report did acknowledge the existence of non-monotonic dose response curves, a step forward from complete disagreement over their existence.

While agencies grappled with whether low dose response impacted their mandate, popular media grappled with the increasingly fractured endocrine disruptor field. Throughout the early 2000s, vom Saal was savaged in several publications (Milloy 2001; Butterworth 2014; Shannon 2008; Fagin 2012). Steve Milloy, in an article for Fox News, called vom Saal a "cult leader" and claimed that vom Saal's lab mice were interbred to the point of being useless (Milloy 2001). An article in *Forbes* mocked vom Saal's portrayal as "a cross between Tiresias and Helen of Troy," sarcastically implying that vom Saal was far from prophetic and that he launched an unnecessary war on BPA (Butterworth 2014). Vom Saal did not take such criticism lying down, calling out industry and the "Third World" regulations of the US, while also rallying like-minded scientists to issue a consensus statement in 2007 (Shannon 2008; vom Saal et al. 2007). In that statement, the researchers stated that, "[c]oncern regarding exposure throughout life is based on evidence that there is chronic, low level exposure of virtually everyone in developed countries to BPA" (vom Saal 2007). They noted that current testing mechanisms did not account for BPA.

Though vom Saal was certainly villainized by industry and skeptics of the endocrine disruptor concept and the low dose concept, he won in the court of public opinion. His research showing the risk of BPA exposure spurred wide scale public

concern over the use of BPA, particularly in baby bottles. Vom Saal played into the heroism, interviewing with the Environmental Working Group and *Mother Jones* (Shannon 2008; Blake 2014a; Blake 2014b). By 2009, public boycotts resulted in the removal of BPA from baby bottles, and as of 2018, many plastic products are prominently labeled "BPA Free," as testament to the success of vom Saal's work to affect social change.

The case of BPA characterizes the third era of scientific discussion of endocrine disruptors. The apparent polarization of the second era came to an end, to be replaced by a very strong animosity between the two sides of the endocrine disruptor debate. Few, if any, researchers maintained a moderate position on BPA and the 'conversation' between either side was harsh and not particularly fruitful.

Conclusion

The third era of discussion continues into the modern day. Endocrine disruptor literature published in 2018 frequently includes digs at opposing viewpoints or long descriptions of the best ways to bring together a fractured field—usually either by abandoning endocrine disruptor research all together or accepting that endocrine disruptors exist and are damaging (Vandenberg et al. 2009; Vandenberg et al. 2012; Zoeller et al. 2014; Nohynek 2013; Lamb et al. 2014).

As of 2018, researchers studying endocrine disruptors remain in two camps: those who think endocrine disruptors pose a threat to humans and those who do not. Each group investigates largely the same question of generally how do endocrine disruptors work. Each group especially works to establish cause (exposure to endocrine disruptors)

and effect (development of adverse health effect). Debate over non-monotonic dose response curves and low dose effects continues, serving as two major fighting points over whether endocrine disruptors pose a threat to human health (Vandenberg et al. 2009; Vandenberg et al. 2012; Rhomberg and Goodman 2012; NRC 2014). Relatively little has changed in terms of opposing viewpoints since 1997.

Recently, the fractured nature of the scientific community around endocrine disruptors has played out most clearly in discussions of how to regulate endocrine disruptors in the European Union (EU), and in particular how to define endocrine disruptors for regulation. In 1999, the European Commission responded to public pressure to regulate endocrine disruptors with a "Strategy for Endocrine Disruptors" (European Commission 1999). In the strategy, the Commission made research cooperation its short-term goal, leaving the development of testing methods and regulations for further in the future, perhaps reflecting a better awareness of the scientific dissidence over endocrine disruption (European Commission 1999).

In the short term, research cooperation did not come about, but in 2009 (and again in 2012) the EU passed regulation that established consequences for use of endocrine disruptors in biocides and plant protection products (European Commission 2018a). In both pieces of legislation, the EU required the Commission to develop "scientific criteria for the determination of endocrine-disrupting properties" (European Commission 2016, 2). In other words, to decide on the definition of endocrine disruption in order to direct regulatory efforts. The deadline for that decision was 2013. The Commission failed to meet that deadline. By 2015, a Court of Justice of the European Union ruling forced the

Commission to reconfirm their work toward a definition and promise a draft by the summer of 2016 (European Commission 2016, 3).

In June 2016, the Commission released their definition, one from a 2002 meeting of the World Health Organization (WHO) on the "Global Assessment of the State-of-the-Science of Endocrine Disruptors" (WHO 2002). The Commission defined an endocrine disruptor as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations," where adverse effect is further defined as "change in the morphology, physiology, growth, development, reproduction, or, life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences" (European Commission 2016, 4–5; WHO 2002, 1). The definition and associated criteria was met with immediate backlash from endocrine disruptor researchers and environmental groups who claimed that the definition set the standard for establishing endocrine disruption impossibly high (*Neslen* 2016). Industry also complained due to the Commission's decision to exclude potency as part of identification (Paun 2018). As of 2018, the Commission's definition has not been agreed upon by the EU Parliament, meaning that member states have not adopted the proposed criteria (European Commission 2018a).

The continued debate in the EU over the definition of endocrine disruptors and how to assess dangerous endocrine disruption is reflective of many of happenings detailed in this dissertation. In Chapter 4, I showed how the scientific community could not come to a consensus on the endocrine disruptor concept in the 1990s, and in this

chapter, I have shown how the intervention of societal actors in the endocrine disruptor discussion polarized the endocrine disruptor community in the US. That polarization has become international, leaving countries trying to establish regulations for endocrine disruptors fighting a losing battle. There is no scientific consensus, and the absolute beliefs held by many endocrine disruptor researchers makes discussion difficult. Regulators, in looking for an agreed upon and scientifically supported definition to focus their regulation, find none.

Social actors have played a role in the scientific polarization of 2018. As I have argued in this chapter, had popular media not mainstreamed the endocrine disruptor concept in 1993, the concept may very well have languished at the scientific fringe or been subsumed into the continuing conversation on environmental estrogens. Had industry and government not intervened in 1996, the endocrine disruptor field may not have polarized to such a degree, where studying endocrine disruptors becomes a political endeavor. Social factors provoked scientific response. In an age where media, industry, and government play such a large role in the conduct and presentation of science, it is necessary to consider the role of societal actors.

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CHAPTER 6

HOW THE SCIENCE OF ENDOCRINE DISRUPTORS MADE ITS WAY INTO REGULATION

INTRODUCTION

When proponents introduced the endocrine disruptor concept in 1991, they made clear that one of their main goals was to get endocrine disruptors regulated. In their statement, they laid out clear regulatory goals, and the concept itself was not only scientific and social, but also regulatory. The legwork proponents did in situating the endocrine disruptor concept in three different spheres ultimately helped them get the substances regulated. Throughout the 1990s, proponents took advantage of the scientific, social, and regulatory appeal of endocrine disruptors, playing actors in each area off each other and cultivating a particular narrative in each area. In this chapter, I explore how proponents of the endocrine disruptor concept used a series of social and political circumstances, along with a carefully crafted scientific narrative, to get the empty concept of endocrine disruptors regulated in 1996 with the Food Quality Protection Act and the Safe Drinking Water Act Amendments.

In this chapter, I advance a two-part argument to explain how endocrine disruptors came to be regulated in the US. The first part deals with the regulatory landscape in the early 1990s that significantly aided proponents of regulating endocrine disruptors. That landscape was dominated by four circumstances: 1. The revision of pesticide regulation in the US through the demise of the Delaney clause, 2. The environmental emphasis of the Clinton administration and the receptiveness of several

EPA administrators to the endocrine disruptor concept, 3. The wider social fear of breast cancer incidence as something that was increasing and stealing the lives of loved ones, and 4. The growing awareness of development as easily perturbed and therefore infants and children as a vulnerable group that needed pesticide regulations to protect them. Each of those circumstances increased the probability that an endocrine disruptor screening program could be passed in the US by either lowering the barriers to such a passage or by increasing social pressure to regulate endocrine disruptors.

However, that window of opportunity in the early 1990s would not in itself have resulted in the regulation of endocrine disruptors. Proponents of regulating the substances had to take advantage of the opportunity and advance a narrative about endocrine disruptors that fit. They did that partially through a public campaign in the media to portray endocrine disruptors as substances that would detrimentally impact all of our lives, as discussed in other chapters. But much of their work took place in Congressional hearings, where they could explicitly use scientific evidence to argue for a particular kind of regulation.

In the early history of endocrine disruptors, five relevant hearings with proponents of regulating endocrine disruptors advanced a very narrow set of scientific facts, especially emphasizing that endocrine disruptors cause breast cancer and disrupt development, in order to solidify the empty category of endocrine disruptors in particular ways. As I pointed out in Chapter 3, proponents of the concept crafted the endocrine disruptor category in broad strokes, leaving out important details like how to identify endocrine disruption. But during the hearings leading up to the passage of the Food Quality Protection Act, proponents solidified the concept in carefully selected ways that

left the impression that endocrine disruptors had been conclusively and causatively connected to effects like breast cancer and declining sperm counts. In that way, proponents took advantage of the unique window of opportunity to reinforce the idea that endocrine disruptors must be regulated.

The result of both the window of opportunity and the inclusion of very specific science was the Endocrine Disruptor Screening Program, the only regulation of endocrine disruptors in the US. In this chapter, I give a brief overview of the regulation, before walking through the four circumstances that combined to enable its passage. Then I detail the hearings through which endocrine disruptors were regulated, paying special attention to the science presented at each hearing as well as the attendees presenting the science. Finally, I highlight some general trends across the hearings to demonstrate the inclusion of very specific scientific facts.

Endocrine Disruptor Screening Program

The Endocrine Disruptor Screening Program was established in 1996 with passage of two federal bills: the Food Quality Protection Act of 1996 and the Safe Drinking Water Act Amendments of 1996 (Pub. L. 104–170, 7 USC § 136 et seq.; Pub. L. 104–182 § 1316). For the purposes of this chapter, I focus on the Food Quality Protection Act as it was passed first, each Act contained the same language, and most of the discussion of endocrine disruptors centered around the Food Quality Protection Act.

The regulation of endocrine disruptors comes from a single section within the larger Act. That section states:

ESTROGENIC SUBSTANCES SCREENING PROGRAM.-

(1) DEVELOPMENT.-Not later than 2 years after the date of enactment of this section, the Administrator shall in consultation with the Secretary of Health and Human Services develop a screening program, using appropriate validated test systems and other scientifically relevant information, to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect as the Administrator may designate. (Pub. L. 104–170, 7 USC § 136 et seq.)

In essence, the Act mandated that the EPA establish a program to test for hormonal activity in new chemicals. Notice that the language of the Act does not specifically require the establishment of an endocrine disruptor screening program, only an estrogenic substances screening program. Nor does it use the term endocrine disruptor. The incorporation of the term into the final EPA program was due to the behind the scenes work of Lynn Goldman and, to a lesser extent, Carol Browner (Krimsky 2000; EPA 1996d; EPA 1996e; EPA 1996f). Both high ranking EPA officials, Goldman and Browner integrated the idea of endocrine disruptors and their testing into the EPA long before the passage of the Food Quality Protection. As discussed later in this chapter, Goldman and Browner served as administration insiders for the endocrine disruptor concept and proponents of regulating the substances.

The section requiring a screening program was a last-minute addition to a much larger bill. On the whole, the Food Quality Protection Act reshaped chemical regulation in the US, through the streamlining and standardization of pesticide approvals through

the EPA and mandating health-based standards for pesticide evaluation. The added section on estrogenic substances was only a small piece of a much larger bill. The addition was added the very day that the Act passed in the House and did not appear in any prior versions of this specific bill nor in other food quality bills more generally (H.R. 4739 100th Cong.; H.R. 1725 101st Cong.; S. 2875 100th Cong.; S. 722 101st Cong.; H.R. 2342 102nd Cong.; S. 1074 102nd Cong.; H.R. 2597 102nd Cong.; H.R. 3216 102nd Cong.; S. 331 103rd Cong.; H.R. 872 103rd Cong.; S. 1478 103rd Cong.; H.R. 4091 103rd Cong.; S. 2084 103rd Cong.; H.R. 4362 103rd Cong.).

The version of the Food Quality Protection Act that passed in 1996 was first introduced in 1995 by Thomas J. Bliley Jr., a Republican Representative from Virginia (H.R. 1627 104th Cong.). H.R. 1627 went through two committees and was amended twice before passage (H.R. 1627 104th Cong.; H.R. 1627 IH, RH, RDS, EH; Committee on Agriculture 1996; Committee on Commerce 1996). Because hormonally active chemicals, estrogenic substances, endocrine disruptors, and reproductive or developmental toxicity were not mentioned in any previous versions of the bill, I will not be dealing with any previous versions in this chapter.[23]

[23] Only one Congressional bill prior to the Food Quality Protection Act included language mandating the testing of estrogenic chemicals, the Pesticide Reform Act of 1994 introduced by California Representative Henry Waxman. Waxman's bill had no cosponsors and was referred to the House Energy and Commerce Subcommittee on Health and Environment, which did nothing with it (H.R. 4362 103rd Cong.). Waxman played a pivotal role in getting endocrine disruptors regulated, as discussed elsewhere in this chapter. His 1994 bill was a first attempt, but because it died well before any meaningful discussion of it took place, I will not cover it in this chapter.

PART I: A WINDOW OF OPPORTUNITY

The first part of my argument regarding how the Endocrine Disruptor Screening Program was enacted deals with a unique window of opportunity in the 1990s that significantly increased the likelihood that something like the program could be passed. In the US, regulatory overhaul like that of the Food Quality Protection Act and the Endocrine Disruptor Screening Program is relatively rare, with most changes in regulation being more incremental. That makes the passage of the Program something worthy of explanation.

The passage of the Endocrine Disruptor Screening Program was enabled by a set of four circumstances, all of which increased the likelihood that such a thing could pass. The first two set of circumstances were specific governmental changes that lowered barriers to the passage: the demise of the Delaney clause and a receptive Clinton administration. The second two circumstances both increased the attention paid to endocrine disruptors, and therefore increased the pressure to and benefit of doing something to address them. I walk through each circumstance below.

The Demise of the Delaney Clause

The first circumstance that increased the probability that an endocrine disruptor screening program would pass in Congress came out of several decades of legal and judicial maneuvering. By the 1990s, Congress was put in a position of having to change regulation of chemicals due to a 1958 clause in the Federal Food, Drug, and Cosmetic Act (Pub. L. 75–717, 21 USC § 301 et seq.). In order to establish how that came about, I

go back and detail that initial clause, the Delaney clause, and its implementation in the three decades between its passage and its removal.

The first regulation of food in the US came in 1906, riding a wave of concern regarding the safety of meat products after the publication of Upton Sinclair's novel *The Jungle* (Sinclair 1906; Greenberg 2016). In 1906, Congress passed the Food and Drugs Act of 1906 (34 Stat. 768), which forbade the marketing of products that "contain[ed] any added poisonous or other added deleterious ingredient which may render [the food] injurious to health" (34 Stat. 768, 770). The Act granted the newly formed Food and Drug Administration[24] (FDA) the ability to punish violations of the policy after the fact, but no ability to regulate production of food and drugs prior to marketing. The Food and Drugs Act of 1906 was the first attempt by the US government to regulate threats to food safety, which was in turn part of a progressive movement to regulate products that affected public health (Merrill 1997).

The 1906 Food and Drugs Act (also known as the Pure Food and Drugs Act) was revised in 1938 as part of Franklin D. Roosevelt's New Deal. The revision, titled the Federal Food, Drug, and Cosmetic Act of 1938 (FFDCA), was in direct response to the marketing of Elixir sulfanilamide, a therapeutic agent that resulted in the deaths of more than 100 people, poisoned by the improperly prepared product (Merrill 1997). The 1938 Act reinforced the FDA's role as a policing agency and bolstered the FDA's capacity

[24] The Food and Drug Administration was not known as the Food and Drug Administration until 1930. However, the federal agency that we now know as the Food and Drug Administration can trace its origin to the Food and Drugs Act of 1906. For purposes of clarity, I will refer to the predecessor agency as the FDA.

(and the US government's ability more broadly) to regulate consumer products that could harm public health.

In 1958, Congress amended the Federal Food, Drug, and Cosmetic Act, passing the Food Additives Amendment of 1958. The 1958 Amendment broadly required FDA approval for all new food ingredients and food-contact materials like packaging. However, the Amendment contained one clause that significantly changed food and pesticide regulation in the US. Within the Food Additives Amendment, the Delaney Clause states,

> … No additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal ... (52 Stat. 1041, 1785)

In short, the Delaney clause precluded the FDA from approving any chemical that could be carcinogenic when fed to animals or humans. As many noted at the time of its passing, the Delaney clause was widely problematic, not least of which because most chemicals on earth can be shown to be carcinogenic in animals under the right circumstances (Degnan and Flamm 1995, 237). That meant that under strict interpretation of the Delaney clause, no chemical could be approved, which would make industry in the US difficult.

In the early 1960s, the widespread use of one particular substance underlined the issues with strict interpretation of the Delaney clause. In 1938, researchers in the UK synthesized one of the first synthetic estrogens, diethylstilbestrol (DES) (Dodds et al. 1938). DES was inexpensive to produce and highly effective as an estrogen mimic

(Abboud 2015). Throughout the 1940s, several studies demonstrated that administration of DES to livestock animals, like cows and chickens, resulted in increased size and improved feed conversion (the efficiency with which livestock convert feed to increased body mass) (Lorenz 1943; Dinusson, Andrews, and Beeson 1948; Dinusson, Andrews, and Beeson 1950; Raun and Preston 2002). As a synthetic estrogen, DES acted as a growth hormone for chickens and cows. By 1954, the FDA approved oral administration of DES in beef cattle, and in 1957, the agency approved the use of DES implants (compressed tablets placed subcutaneously) in cattle (Raun and Preston 2002). Uptake of DES as a growth hormone in livestock was rapid. By the 1960s, DES was the most common growth promoter used in the US (Marcus 1994; Epstein 1990). Upwards of 95 percent of cattle were fed DES over their lifetimes, meaning that much of the livestock industry relied on its use (Marcus 1994).

However, DES should not have been approved for use under the Delaney clause. Several studies throughout the 1950s demonstrated the carcinogenic effects of DES at high doses, particularly in estrogen-sensitive tissues like mammary tissue (Bern 1960; Gardener 1939; Cole et al. 1975). Such studies should have disqualified the use of DES, but the carcinogenicity of DES was less than clear cut. Additional studies of DES indicated that the chemical was not carcinogenic at low doses, leaving many researchers questioning whether the doses of DES given to livestock would increase cancer rates in the animals (Marcus 1994). Additionally, detection methods in the 1950s and 1960s could not detect DES in the meat from DES-fed livestock, apparently abrogating any risk to humans (Raun and Preston 2002). Though under strict interpretation of the Delaney

clause, the FDA should have barred the use of DES, they instead relied on the lack of residues in meat to support the continued use of DES.

To codify that policy, in 1962, the FDA proposed (and Congress passed) the DES proviso (Committee on Pesticide Use Patterns 1987; 21 U.S.C. 360b(d)(1)(I)). The DES proviso stated that the FDA did not have to apply the Delaney clause to carcinogenic drugs or feed additives given to livestock as long as the agency could show that the substances could not be found in the resulting meat. In essence, the assumption was that as long as the carcinogens could not be detected in products, then the products could not pose any risk to public health.

The DES proviso allowed the FDA to continue to approve the use of DES in livestock until the 1970s. By the 1970s, though, improved sensitivity of detection tests made clear that any administration of DES during life resulted in residues after slaughter (Merrill 1997). The resulting residues invalidated the FDA's work-around of the Delaney clause. Additionally, in 1971, the work of Arthur Herbst and Robert Scully revealed DES as a potent human carcinogen, increasing scrutiny of its use in livestock (Raun and Preston 2002; Herbst and Scully 1970). Thus began the FDA's (and later the EPA's) two-decade effort to evade the Delaney clause.

In order to allow for the continued use of DES, as well as many other chemicals used in food production, the FDA adopted a quantitative risk assessment protocol for chemical residues in food (Committee on Pesticide Use Patterns 1987). Under the protocol, the FDA approved carcinogenic chemicals as long as sponsors could demonstrate that the resulting residues did not increase lifetime cancer risk by more than 1 in 1,000,000 (1×10^{-6}) (Committee on Pesticide Use Patterns 1987; Merrill 1997). Not

only did that pacify the agricultural industry, which had come to rely on a wide range of chemicals, but it more generally made the Delaney clause practical to enforce.

The FDA's numerical contortion did not go unnoticed, especially given the increased attention paid to industrial and agricultural chemicals with the growing environmental movement. Environmental groups brought numerous challenges to the FDA's enforcement of the Delaney clause throughout the 1970s (*Environmental Defense Fund, Inc. v. DHEW* 1970; *Environmental Defense Fund, Inc. v. Ruckelshaus* 1971; *Chemetron Corp. v. DHEW* 1974; *Hess & Clark, Division of Rhodia, Inc. v. FDA* 1974). Organizations like the Environmental Defense Fund repeatedly lost the cases as judges deferred to the FDA on the best way to interpret and apply the Delaney clause (*Environmental Defense Fund, Inc. v. DHEW* 1970; *Environmental Defense Fund, Inc. v. Ruckelshaus* 1971). Such deferral fits into a much larger narrative about the relationship between federal agencies and the judicial branch in light of the Administrative Procedures Act of 1946, which is not relevant for this chapter (Pierce 1996; Shapiro 1996). What is relevant is that by the 1980s, courts had ceased to defer to the FDA on appropriate enforcement of the Delaney clause and instead repeatedly referred to the explicit language of the clause itself (*Rhone-Poulenc, Inc., ETC. v. FDA* 1980; *Scott v. FDA* 1984; *Public Citizen v. DHHS* 1986; *Public Citizen v Young* 1987; *Public Citizen v. Bowen* 1987; *Simpson v. Young* 1988; *Nader v. EPA* 1988). Federal courts vacated FDA approvals of several new chemicals in the late 1980s[25] due to strict interpretation of the

[25] Cases in the 1980s dealt both with new pesticides as well as with color additives.

Delaney clause in court. Those cases signaled the beginning of the end of the Delaney clause as a viable regulation.

That end came quickly in the 1990s with decisions in three California court cases: *California v. Reilly* (1990), *Les v. Reilly* (1992), and *California v. Browner* (1994). Each case was brought against the EPA, which had replaced the FDA in regulating pesticides following its creation in 1970. In each case, decided subsequently in 1990, 1992, and 1994, courts required the EPA to apply the Delaney clause to an increasing number of pesticides, until the decision in the 1994 case *California v. Browner* required the EPA to revoke approval for 121 pesticide/crop combinations (*California v. Browner* 1994; Merrill 1997). If the EPA had in fact barred the use of so many pesticides, the agricultural industry in the US would have been severely impacted. Because of that, the decision in *California v. Browner* necessitated the replacement of the Delaney clause.

The necessity of leaving behind the Delaney clause did not go unnoticed by Congress. Beginning in 1990, many Congressional representatives proposed bills to overhaul the regulation of chemicals in the US (H.R. 4739 100th Cong.; H.R. 1725 101st Cong.; S. 2875 100th Cong.; S. 722 101st Cong.). Both Democrats and Republicans suggested a number of solutions, but the bills failed to generate any sense of urgency. However, *California v. Browner* increased the need to get some sort of bill passed, especially after 1994. A new system for regulating food-related chemicals (pesticides, chemicals used in food packaging, food additives, etc.) was going to be passed before 1997, when the *Browner* decision had to be implemented.

The fact that such a reorganization was going to occur created an opening for proponents of regulating endocrine disruptors. Proponents like Colborn wanted to see

endocrine disruptors regulated. Total overhaul of regulations in the US is quite rare; most changes are more incremental. If Colborn and others could convince enough representatives of the need to regulate endocrine disruptors and that regulation was incorporated into the larger changes to chemical regulations, then proponents had a better than normal chance of getting an endocrine disruptor screening program on the books. The demise of the Delaney clause and the anticipated reconceptualization of chemicals approval was one of a series of circumstances that increased the probability of regulating endocrine disruptors in the early 1990s.

A Receptive Clinton Administration

The second circumstance of proponents' window of opportunity became clear in 1993. Bill Clinton was sworn in as 42nd president of the US on 20 January 1993, along with his vice president, Al Gore. Clinton came to the White House with a poor environmental record (*NYT* 1993; Vogel 2012). As governor of Arkansas, he worked closely with the poultry industry, heavy polluters in the state. He admitted to overlooking pollution to charm industry and bring jobs to his poor state (*NYT* 1993). However, his selection of Gore as his running mate gave many environmentalists hope that his presidency would be different (*NYT* 1993; Ifill 1992). Gore passionately supported environmental issues during his time in Congress and it appears Clinton and his campaign specifically selected Gore to appeal to an increasingly environmentally-conscious electorate (Ifill 1992).

After inauguration, Gore seemed to have an outsize effect on Clinton and his administration. Clinton, on the campaign trail and in office, emphasized that

environmental regulations need not eliminate jobs and that he was committed to a cleaner America (Schneider 1992). More concretely, Clinton appointed several environmental sympathizers to key positions, including Bruce Babbitt, former governor of Arizona (Friedman 1992).

Most importantly for endocrine disruptors, Clinton appointed Carol Browner, Florida Secretary of Environmental Regulation and Gore student, as Administrator of the EPA and Lynn Goldman, a pediatrician from California's Department of Public Health, as Assistant Administrator of the Office for Prevention, Pesticides, and Toxic Substances (Friedman 1992). Both women were aware of endocrine disruptors and their potential impact on health. As told by Goldman in her foreword to Sheldon Krimsky's *Hormonal Chaos*,

> The endocrine disrupter issue was at the center of my radar screen from the first day of my term (1993–1999) … Such was the sense of urgency attached to the issue that, one day in October 1993, EPA Administrator Carol Browner was asked to swear me into office on an urgent basis so I could testify before a hearing of a subcommittee of the House Government Oversight Committee about estrogens in the environment … The testimony [of the scientists at the hearing] … convinced me that the issue should become a priority for the EPA's chemical and pesticide programs. (Krimsky 2000: vii–viii)

Goldman and Browner were both aware of endocrine disruptors as a new category of toxic substances and believed that the EPA should play a large role in their regulation. Goldman had conducted a significant amount of research in California on the impact of pesticides on the health of children and testified in 1991 on "Government Regulation of

Reproductive Hazards" (Goldman et al. 1985; Paigen et al. 1987; U.S. Congress Senate 1991, Testimony of Lynn Goldman). Colborn introduced endocrine disruptors for the first time at the same hearing (U.S. Congress Senate 1991, Testimony of Theo Colborn).

Clinton's election and appointments created a receptive environment for the science and regulation of endocrine disruptors. Both Browner and Goldman saw it as a priority—not simply reorganizing pesticide regulation in the US, but more specifically addressing hormonally active agents and their impact on children and infants. Gore was also aware of endocrine disruptors, writing the preface for Colborn's book, *Our Stolen Future*, in 1996 (Colborn, Dumanoski, and Myers 1997). For proponents of the regulation of endocrine disruptors, the Clinton administration's awareness and belief in the problem of endocrine disruptors meant they had sympathetic ears inside an administration that sought to make a mark on environmental regulation in the US.

Such a welcome, in combination with the changes occurring to chemicals regulation, created a unique moment in history whereby novel legislation regarding a new category of toxic substances could be passed, if the right people were spoken with and the right science emphasized. The receptive Clinton administration formed the second of four circumstances that together enabled the implementation of the Endocrine Disruptor Screening Program.

Widespread Fear of Breast Cancer

The final two circumstances that increased the probability of endocrine disruptor regulation differed slightly from the first two. While the demise of the Delaney clause and the receptive Clinton administration were specific governmental changes, the

widespread fear of breast cancer and the growing awareness of development as a vulnerable time were more general trends that created strong social pressure on legislators to act.

A vast amount of social pressure grew out of the focus on breast cancer in the 1990s. In 1990, experts estimated that one in ten women in the US would develop breast cancer, a 25 percent increase[26] from the 1980s (Andsager and Powers 1999; Kahi and Lawrence-Bauer 1996). That increase, along with the work of several non-profit breast cancer groups, brought attention to the disease. Women's magazines like *Ladies Home Journal* and *Ms.* intensified their coverage of breast cancer by 33 percent and news sources like *TIME* and *Newsweek* also published more stories on breast cancer (Andsager and Powers 1999).

A number of other happenings in the 1990s grew the attention to breast cancer still further. In 1990, Medicare began covering biannual mammograms for women, meaning that more women discussed breast cancer with their physicians as part of their annual care (Beck et al. 1990; Andsager and Powers 1999). That same year, at the University of California, Berkeley, Mary-Claire King discovered the *BRCA1* gene, associated with breast and ovarian cancer (Hall et al. 1990). In 1991, the newly formed National Breast Cancer Coalition started a grassroots campaign to increase funding for

[26] Information on the increased incidence of breast cancer in the 1990s varies, with some postulating that it was only a 15 percent increase while others indicate that the increase could have been closer to 30 percent (Glass et al. 2007). However, the actual value matters less than the fact that there was widespread public belief that rates had increased significantly and that the lives of many women were threatened by the increase.

breast cancer research (Gorman 1993). All of those occurrences heightened the general public's knowledge and fear of breast cancer.[27]

In short, much of the public and Congress was familiar with breast cancer as a modern problem and many demanded action. Clinton's voice joined the demand for action after his mother was diagnosed with breast cancer (Osuch et al. 2012). She died in 1994 from the disease (Osuch et al. 2012). The social pressure to act to stem the flow of mothers, wives, sisters, and daughters affected by breast cancer was high.

Action took many forms, including an increased budget for breast cancer research from the National Cancer Institute and the passage of several bills emphasizing women's health (Osuch et al. 2012). But it also took the form of regulating endocrine disruptors. As I will discuss in part II of this chapter, much of the expressed logic for regulating endocrine disruptors was as a means to reduce the incidence of breast cancer in the US. The public fear and pressure to act on breast cancer made up the third circumstance that enabled the passage of endocrine disruptor regulation.

Awareness of Development as Vulnerable to Perturbation

Awareness of development as a special or different time for the toxicity of chemicals was the final circumstance that created the window of opportunity through

[27] It is important to point out here that much of the public feared breast cancer as a disease that could steal their female family and friends from them and also feared breast cancer risk and all the invisible, unknown, and subtle factors that could add to that risk. Proponents, in their work with public news media and at Congressional hearings, clearly established endocrine disruptors as one of those factors that significantly increased an individual's risk of developing breast cancer, thereby using the ides of risk in the public imagination to their advantage.

which endocrine disruptors were regulated. That awareness had grown throughout the second half of the twentieth century, with the realizations about thalidomide and DES, but reached a new level in the early 1990s following the release of a report from the National Research Council.

In 1988, at the request of Congress, the National Academy of Sciences established a committee to examine the effects of pesticides in the diets of infants and children[28] (Committee on Pesticides 1993). The committee released their report in 1993. In the report, the committee highlighted the important difference between a fully mature adult and a developing sub-adult: "children are not little adults" (Committee on Pesticides 1993, 3). Most, if not all, chemical testing and regulation at the time assumed that those exposed to chemicals would be fully grown adults, meaning that they did not account for the varying vulnerability of still-developing humans (Committee on Pesticides 1993). The committee's main finding was in line with that, namely that infants and children differ qualitatively and quantitatively in their exposure to pesticides in food and their susceptibility to the toxicity of those pesticides. They recommended strong changes to pesticide regulation to reflect that.

The National Academy report received widespread media coverage, not only in larger newspapers like *The New York Times* but also in local newspapers and news broadcasts (Burros 1993). Parents in the US were inundated with the information that pesticides could threaten the health of their children. Many environmental groups hyped

[28] The Committee on Pesticides in the Diets of Infants and Children defined infants and children as any individual between twenty-six weeks' gestation and eighteen years old (Committee on Pesticides 1993, 2–3).

the report, adding to the coverage. The Environmental Working Group (EWG) published their own report, just days after the National Academy published theirs (Burros 1993). In the EWG report, the organization claimed that a child in the US received the acceptable lifetime doses of eight pesticides within the first year of life (Burros 1993). That report also received quite a bit of coverage.

The National Academy report and the attention it brought to development as a sensitive time was the last circumstance that combined to create an opening for the regulation of endocrine disruptors. The idea of developing organisms as more easily perturbed by toxic chemicals fit into the narrative that many were already telling about endocrine disruption. Endocrine disruptors were those chemicals doubly affecting children and infants. The fear of breast cancer and the awareness of development both influenced the science used by proponents to argue for regulating endocrine disruptors.

The regulation of endocrine disruptors in 1996 was passed as a result of unique circumstances in the early 1990s. In particular, two governmental changes and two larger social trends combined to create a window of opportunity for proponents of the endocrine disruptor concept, whereby there was both a mechanism for passing legislation and a significant amount of social pressure that made doing so beneficial for representatives. Without the set of four circumstances, it is unlikely that the US would have regulated endocrine disruptors in the 1990s. The European Union, generally the more cautious of the two regulatory systems, did not release a statement on endocrine disruptors until 1999 and earlier bills proposing to reform the chemical regulation in the US make it clear that no one within Congress was thinking to regulate endocrine disruptors (H.R. 4739 100th Cong.; H.R. 1725 101st Cong.; S. 2875 100th Cong.; S. 722 101st Cong.; H.R. 2342 102nd

Cong.; S. 1074 102nd Cong.; H.R. 2597 102nd Cong.; H.R. 3216 102nd Cong.; S. 331 103rd Cong.; H.R. 872 103rd Cong.; S. 1478 103rd Cong.; H.R. 4091 103rd Cong.; S. 2084 103rd Cong.; H.R. 4362 103rd Cong.). The statute that created the Endocrine Disruptor Screening Program was a last-minute addition after Committee review. It was not popular among industry groups. A significant segment of the scientific community disagreed with the regulation. The Endocrine Disruptor Screening Program is a bit miraculous and part of that is due to the four circumstances outlined above: 1. The demise of the Delaney clause, 2. The receptive Clinton administration, 3. The fear of breast cancer, and 4. The growing awareness of the vulnerability of infants and children.

PART II: INCLUSION OF SELECT SCIENCE TO SOLIDIFY ENDOCRINE DISRUPTORS

However, those four things on their own would not have resulted in the creation of the Endocrine Disruptor Screening Program. All four changes only created an opening that had to be taken advantage of by proponents of regulating endocrine disruptors. As I have detailed in other chapters, those proponents were largely scientists turned activists who worked diligently in public and regulatory spheres to tell a narrative about endocrine disruptors that prompted action. Environmental groups also took up that task. Groups like the National Resource Defense Council, the National Coalition Against the Misuse of Pesticides, and the EWG released their own public statements and participated actively in many of the hearings on endocrine disruptors.

The scientists and environmental groups that pressed for regulation of endocrine disruptors capitalized on the opportunity created in the early 1990s by pushing a particular set of what they saw as scientific facts, backed up by a select number of

studies. The science that was incorporated into the regulation was controlled by those individuals and fit in neatly to the fears and trends of the time. In that way, proponents used the tripartite nature of the endocrine disruptor concept to push for their ultimate goal. Because they situated the concept in scientific, social, and regulatory arenas, proponents could use evidence or capital from all three to push for regulation. They used select science that corresponded to social trends of the time allowing them to use both the weight of the scientific evidence as well as the social capital from acting on things like breast cancer and developmental threats. By presenting both the science and the social awareness in Congressional hearings, proponents put pressure on regulators to act on topics their constituency cared about. The work proponents did in Congressional hearings leading to the regulation of endocrine disruptors was really the culminating piece in making the endocrine disruptor concept scientific, social, and regulatory.

The science used by proponents at the Congressional hearings detailed in this chapter served a second purpose, beyond connecting to social trends. Proponents used specific studies to solidify the endocrine disruptor category in key ways. When the category was initially presented in 1991, proponents outlined some broad characteristics of endocrine disruptors, but largely left the categorical box empty. They did not lay out what chemicals should be included as endocrine disruptors, how to identify endocrine disrupting chemicals, or through what mechanisms endocrine disruptors functioned. In those ways, the category of endocrine disruptors was not real or solid enough to regulate. However, through their work at Congressional hearings, proponents solidified the concept enough by connecting the category to larger public health threats like breast cancer and sperm count declines. Proponents used specific studies to answer the question

of "What are endocrine disruptors?" The studies they used showed that endocrine disruptors are chemicals that cause breast cancer, and chemicals that cause sperm declines, and chemicals that threaten the health of children. Those answers politically reified the endocrine disruptor category, in so far as it placed particular effects in the endocrine disruptor category box that convinced regulators of the need to regulate the category. That, in combination with their situation of the endocrine disruptor concept, ultimately led to the regulation of endocrine disruptors.

To show that, I examine the five Congressional hearings relevant to endocrine disruptors. The hearings are all explicitly about regulating toxic chemicals, meaning that the scientific evidence presented in the hearings is unambiguously to spur regulation (or to hinder it). The five hearings are also instances when the different stakeholders interested in whether endocrine disruptors would be regulated directly interacted. At the hearings, industry group representatives were asked the same questions as environmental group representatives as activist scientists as government agency representatives. The differences in their answers reveal tensions over the endocrine disruptor concept and category, with the final bill perhaps serving as the score board. To bring out those tensions and to make clear the work of proponents at each hearing, I walk through each hearing, highlighting the science referenced in each, by whom, as well as any other relevant points. At the end, I then draw attention to similarities between the hearings and the overall work of proponents to push for the regulation of endocrine disruptors.

Senate Hearing on "Government Regulation of Reproductive Hazards," 1991

The first hearing relevant to endocrine disruptors took place in 1991, just days after the Wingspread conference (Colborn and Clement 1992). The Senate hearing on "Government Regulation of Reproductive Hazards" was the first instance where the science of endocrine disruptors was presented in a regulatory context and very much set the pattern for later hearings (U.S. Congress Senate 1991, Testimony of Theo Colborn). During the hearing, one proponent began to tie the endocrine disruptor category to key diseases in order to solidify it in a regulatory context while also introducing the endocrine disruptor concept to policymakers for the first time.

John Glenn, Chairman of the Committee on Governmental Affairs, oversaw the hearing, which oriented around a report authored by the General Accounting Office (GAO) (U.S. Congress Senate 1991). Glenn had asked the GAO to investigate whether four government agencies (the FDA, EPA, OSHA, and the CPSC) adequately regulated reproductively hazardous chemicals. The GAO report dictated the testimony of many of the hearing witnesses, which included representatives from the agencies (U.S. Congress Senate 1991, Testimony of Eleanor Chelimsky). Only three other individuals attended as witnesses: Lynn Goldman, then Chief of the Office of Environmental and Occupational Epidemiology in the California Department of Health Services; Theo Colborn, Director of the Toxics in Wildlife Program at The Conservation Foundation; and Donald Mattison, Dean of the Graduate School of Public Health at the University of Pittsburgh. All three were researchers who studied the reproductive effects of industrial and agricultural chemicals. All three had found grave effects as a result of exposure.

The hearing started with a statement by Glenn on the purpose of the meeting. Glenn's statement reveals that a certain set of scientific facts inspired the hearing, scientific facts that picked up on the developmental underpinnings of the endocrine disruptor concept discussed in Chapter 2. Glenn started by mentioning three instances of developmental abnormalities caused by chemical exposures *in utero*: limb deformities caused by thalidomide worldwide, reproductive cancers caused by DES in the US, and neurological abnormalities caused by methylmercury in Minamata, Japan[29] (U.S. Congress Senate 1991, 1). He also highlighted a multiyear study from the Great Lakes region that linked ingestion of polychlorinated biphenyl (PCB) contaminated fish by pregnant women with developmental delays in the resulting children (U.S. Congress Senate 1991, 2).

Glenn's statement is almost entirely about endocrine disruptors, though he did not use that term. In 2018, DES, methylmercury, and PCBs are all recognized as endocrine disruptors (NIEHS 2017b). Glenn's statement makes it clear that he and others were worried about chemicals ingested by pregnant women that could harm fetuses. Congress people like Glenn were perhaps already interested in hearing about a new category of toxic substances that caused such effects and could be regulated as a group.

[29] Methylmercury is a potent endocrine disruptor (Tan, Meiller, and Mahaffey 2009). Glenn referred to an event in Minamata, Japan, where a chemical factory contaminated local water with methylmercury that then bioaccumulated in shellfish and fish (Ekino et al. 2007). Local people exposed directly were diagnosed with Minamata disease, a neurological syndrome characterized by muscle weakness, ataxia, paralysis, insanity, and eventual death. Children exposed to methylmercury *in utero* had a congenital form of the disease, which was initially mistaken as cerebral palsy (Harada 1978).

In her testimony, Colborn[30] played in to those interests, presenting the two-part endocrine disruptor concept and the connecting category as a group of chemicals that seriously threatened the health of children and pregnant women. In her oral testimony, Colborn laid out the concept and category, supplementing her explanation with the Wingspread consensus statement (U.S. Congress Senate 1991, Testimony of Theo Colborn; Colborn and Clement 1992). Colborn then started to create the scientific narrative that would solidify the category and connect the concept to social and regulatory actors. She did that through inclusion of two studies: her work in the Great Lakes region and a study linking PCBs with birth abnormalities (U.S. Congress Senate 1991, Testimony of Theo Colborn; Colborn et al. 1990; Jacobson, Jacobson, and Humphrey 1990). Colborn highlighted her finding linking contaminated fish consumed by pregnant women and rats with negative health effects and the linkage of PCB exposure *in utero* with low birth weight (Colborn et al. 1990; Jacobson, Jacobson, and Humphrey 1990).

The scientific evidence Colborn used in her testimony very much oriented around the effects of endocrine disruptors in children. That emphasis matched the emphasis placed by Glenn in his opening statement and also picked up on the growing trend emphasizing development as a unique process for perturbation by toxic chemicals. In connecting endocrine disruptors to effects in children, Colborn began to pinpoint one

[30] A note on Colborn's presence at the 1991 Senate hearing: In the years prior to 1991, Colborn worked in the Great Lakes region studying the effects of environmental pollution on the wildlife and humans there (Colborn et al. 1990). In his opening statement, Glenn references one of the papers to come out of that research (U.S. Congress Senate 1991). Glenn, as Chairman of the Committee on Governmental Affairs, had helped appropriate funds for Colborn's research in the Great Lakes (Colborn et al. 1990).

aspect of the endocrine disruptor category: that the chemicals within it threaten the health of children. In doing so, Colborn reified the category in a key way for policymakers, who could justify (and politically capitalize on) action on endocrine disruptors based on that connection.

Something else of note in Colborn's testimony: She took pains to presents endocrine disruptor scientists as underdogs fighting for the greater good. In response to a question from Glenn on the organization of research on reproductive hazards, Colborn responded,

> Well, it is very interesting. The only reason I was able to bring these 21 experts together was because I had so much evidence from wildlife around the Great Lakes, and the work that has been done around the Great Lakes has not been generally funded by the Federal Government. It has been work that researchers have been doing on the side through universities on grants, and they have had to bootleg much of the analysis to Japan and to Sweden to get the chemistry done because we don't have the facilities …
>
> So it has been really a network of robust, vital wildlife biologists and toxicologists that have formed the network that led us to the conclusions that we have today. They need help. (U.S. Congress Senate 1991, Testimony of Theo Colborn)

In that statement, Colborn portrayed endocrine disruptor researchers as altruistic, with no hidden motivations, and also called for increased funding for what really was a fringe idea with little support in the scientific community.

The first hearing in which the science of endocrine disruptors played a role left a sense that endocrine disruptors posed a serious threat, particularly to children, and that endocrine disruptor researchers could be trusted. Both were key to the scientific narrative proponents used in the 1990s to get endocrine disruptors regulated.

Joint Hearing on the "Safety of Pesticides in Food," 1993

The second hearing relevant to endocrine disruptors picked up the widespread social concern about breast cancer, pinpointing another aspect of the endocrine disruptor category to make the category real and scary enough to prompt regulatory action. In 1993, the House of Representative's Subcommittee on Health and the Environment and the Senate's Committee on Labor and Human Resources held a joint hearing on the "Safety of Pesticides in Food" (U.S. Congress 1993). The hearing came out of early efforts to reform pesticide regulation in light of issues with the Delaney clause. The hearing started shortly after publication of the National Academy report on pesticides in the diets of infants and children and a failed attempt by the Bush administration to create a Delaney clause exemption (Committee on Pesticides 1993; U.S. Congress 1993).

The 1993 hearing was much broader in focus than the 1991 hearing, interested more generally in pesticide regulation (U.S. Congress 1993). No proponents of the endocrine disruptor concept attended the meeting, and endocrine disruptors were not mentioned explicitly. However, the hearing makes clear the increasing focus on children as a special group for pesticide regulation and the linkage of hormonally active chemicals and breast cancer, both larger social trends that helped to pass endocrine disruptor legislation.

The hearing was overseen by Henry Waxman and Edward Kennedy, who co-sponsored one of the first bills to reform the Delaney clause. Waxman was a Democrat from California and Kennedy, a Democrat from Massachusetts. The hearing was attended by Carol Browner, the new EPA Administrator, David Kessler, the FDA Commissioner, several Congressional representatives, and a representative from the National Resource Defense Council (NRDC) (U.S. Congress 1993, V).

Most of the testimonies focused on the recently released National Academy report and on the carcinogenic properties of many pesticides. As discussed in Chapter 3, regulators were slow to move from cancer endpoints as the pinnacle of toxicity testing. Only one testimony focused on hormonally active chemicals, the testimony of Senator Alfonse D'Amato.

D'Amato was Senator in New York and had taken note of the high breast cancer rates in Nassau and Sulfolk counties (U.S. Congress 1993, Testimony of Alfonse D'Amato). As he stated in his testimony, he believed that the high rates were a result of estrogenic chemicals and pesticides. D'Amato referenced in support of that a 1993 study published by Mary Wolff (Wolff et al. 1993; U.S. Congress 1993, Testimony of Alfonse D'Amato). Wolff conducted a blind study looking for a link between PCB and DDT exposure and breast cancer in 14,290 blood samples from New York University's Women's Health Study (Wolff et al. 1993). Wolff and her colleagues found that blood levels of a DDT metabolite were 35 percent higher in women who eventually developed breast cancer. The authors posited that exposure to estrogenic pesticides like DDT caused breast cancer (Wolff et al. 1993). In his testimony, D'Amato laid out Wolff's study as reason to insert a specific provision in the Food Quality Protection Act that the EPA test

pesticides for estrogenicity (U.S. Congress 1993; U.S. Congress 1993, Testimony of Alfonse D'Amato). Following the testimony of D'Amato, much of the hearing focused on breast cancer, with attendees taking time out of their statements to comment on the need to address breast cancer and how important D'Amato's point was (U.S. Congress 1993).

D'Amato was the first policymaker to suggest that the EPA test specifically for estrogenicity of chemicals. His connection to estrogenic chemicals rather than endocrine disruptors is a result of proponents' inability to control how media presented the endocrine disruptor concept. During the early 1990s, when newspapers began first publishing on endocrine disruptors, journalists largely focused on the feminization caused by such chemicals, meaning that they linked to the estrogenicity of chemicals rather than the much broader hormonal activity of chemicals highlighted by proponents in the endocrine disruptor concept. The feminizing effects of certain chemicals sold a lot of newspapers, and left an indelible connection between estrogenic chemicals and negative effects. That connection was only strengthened by the studies proponents highlighted, which connected endocrine disruptors to breast cancer, sperm count declines, shrinking penises, and other effects perceived as feminizing. As a result, the legislation in the Food Quality Protection Act calls for an estrogenic chemical screening program, rather than an endocrine disruptor screening program. The shift to endocrine disruptors was a result of the work of Browner and Goldman in the EPA, and demonstrates how the work of proponents in Congressional hearings took advantage of a window of opportunity made up of both social trends and sympathizers in key positions.

Though no Wingspread proponents attended the second hearing, their work was clear in the focus on breast cancer. As discussed in Chapter 4, the connection between endocrine disruptors and breast cancer was a key part of proponents' argument that endocrine disruptors threatened human health. They spent time emphasizing Wolff's study in public news and with policymakers they spoke with outside of Congressional hearings. Wolff's study linking estrogenic pesticides with breast cancer was another key way proponents solidified the endocrine disruptor category for policymakers, again connecting the chemicals in the category with a politically actionable disease. The second hearing relevant to endocrine disruptors shows that endocrine disruptors were quickly linked to breast cancer via one study and that that linkage was hugely powerful.

House Hearing on "Health Effects of Estrogenic Pesticides," 1993

The third hearing emphasized that further. In 1993, the House Subcommittee on Health and the Environment held a hearing on "Health Effects of Estrogenic Pesticides" (U.S. Congress House 1993). Within the hearing, proponents continued to reinforce the link between endocrine disruptors and breast cancer while also introducing another study, one showing global sperm declines as a result of exposure to hormonally active chemicals. Both studies helped proponents fill in the endocrine disruptor category but also continued to emphasize the feminizing effects of hormonally active chemicals, which had consequences for the language in the final regulation.

Henry Waxman oversaw the proceedings of this hearing as well. Waxman was a liberal Representative from California who had an interest in the politicization of science. He was involved in the hearings on tobacco, in 1994 getting several tobacco executives to

swear under oath that they did not believe nicotine was addictive (Hilts 1994). In 2003, Waxman authored a report asserting that the Bush administration "manipulated the scientific process and distorted or suppressed scientific findings" on several topic areas, including the toxicity of pesticides generally and one endocrine disrupting chemical in particular, perchlorate (Committee on Government Reform 2003)). Those facts are relevant in so much as they give insight into a man who was instrumental in the establishment of the Endocrine Disruptor Screening Program. Waxman was committed to scientific truth and had experienced the duplicity of the tobacco industry. I would argue that he was predisposed, in many ways, to believe that pesticides were responsible for any number of ills. And he not only oversaw the hearings on endocrine disruptors, but also helped to author the Food Quality Protection Act that regulated them.

In the 1993 hearing, breast cancer was clearly the focus, not just for Waxman, but for all the attendees. Attendees at the hearing included: Mary Wolff, author of the study linking endocrine disruptors and breast cancer; Devra Davis Lee, who authored several articles with Wolff confirming the link; Louise Slaughter, who had secured $500 million for NIH breast cancer research the year before; and Jane Reese-Colbourne, a board member of the National Breast Cancer Coalition (U.S. Congress House 1993). Also in attendance were three Wingspread attendees—Colborn, Ana M. Soto, and Richard Wiles—, a representative from both Greenpeace and the EWG, and two long-time environmental estrogen researchers, Louis Guillette and John McLachlan. A look at the list of testifiers makes it clear that endocrine disruptors would be front and center. And they were.

In the testimonies themselves, several studies came up repeatedly and those studies built on the scientific narrative Colborn had started in the first hearing 1991. Wolff's study on breast cancer and pesticides dominated the proceedings, showing how powerful the connection between endocrine disruptors and breast cancer was (Wolff et al. 1993). Almost everyone who spoke at the hearing talked about breast cancer at length, taking time to mention friends and family who had been diagnosed (U.S. Congress House 1993). Wolff's study was treated as fact by many of the participants—breast cancer is caused by pesticides, or we should at least assume it is and ban them anyway. That Wolff's study had received criticism in the scientific community, both for experimental set up and the inability of others to replicate her findings, was not mentioned (Safe 1994; Safe 1995; Krieger et al. 1994).

Several other studies got repeated mention in the hearing as well: the worldwide declining sperm counts found by Nils E. Skakkebæk and Richard M. Sharpe, the shrinking alligator penises described by Guillette, and Soto's finding of the estrogenicity of endosulfan (Sharpe and Skakkebæk 1993; Guillette et al. 1994; Soto, Chung, and Sonnenschein 1994; Soto et al. 1995). Other chapters in this dissertation detail Sharpe and Guillette's work, so I won't describe them here (see Chapter 4). I will point out, though, that both deal explicitly with what the media dubbed a loss of maleness and that most of Congress is male. Soto's work with endosulfan showed that the commonly-used pesticide caused cell proliferation in breast cancer cell lines (Soto, Chung, and Sonnenschein 1994; Soto et al. 1995). The study itself and endosulfan's effects were referenced several times to indicate the scope of the problem posed by endocrine disruptors.

Testimonies at the hearing focused on Wolff's breast cancer study, the study showing declining sperm counts, and Guillette's findings on shrinking alligator penises. Each study picked up on social trends like fear of breast cancer and men's general fear of loss of virility while also helping proponents to pinpoint aspects of the endocrine disruptor category that would motivate action. Endocrine disruptors threatened the health of babies, increased the risk of breast cancer, and endangered the size and contents of men's reproductive organs. Those became the characteristics of endocrine disruptors, a category that could be regulated to head off those hazards, as presented by proponents. While politically motivating, the studies proponents emphasized also left the impression that the danger of hormonally active chemicals was from their estrogenic effects, rather than their broader hormonal effects, hence the final legislation on estrogenic chemicals rather than endocrine disruptors.

The third hearing makes clear what science was becoming indelibly linked to endocrine disruptors, namely their link to breast cancer and the decline of male fertility. Those links paralleled the attention paid to endocrine disruptors in the media. Though breast cancer and sperm count declines were far from the focus in the scientific study of endocrine disruptors, they were in the spotlight publicly and politically. They also helped proponents to detail what an endocrine disruptor was for regulators. Proponents did not have to rely on intricate scientific explanations, or even the general explanations they offered in the Wingspread consensus statement. Instead, to explain the endocrine disruptor concept and category, all proponents needed to do was mention breast cancer and shrinking penises.

Hearing before House Subcommittee on Department Operations, Nutrition, and Foreign Agriculture on the "Food Quality Protection Act of 1995," 1995

Following the 1993 hearing on the "Health Effects of Estrogenic Pesticides," Thomas J. Bliley Jr., a Republican Representative from Virginia, introduced the Food Quality Protection Act in the House (H.R. 1627 104th Cong.). The original draft of the Act contained no mention of endocrine disruptors or estrogenic pesticides, though it did heavily emphasize children and infants (H.R. 1627 104th Cong., IH, RH, RDS, EH). Between the third hearing and the fourth hearing relevant to endocrine disruptors, both the House and the Senate went from Democrat hands to Republican hands. However, change to the chemical approval system in the US was widely bipartisan, with Waxman, a Democrat from California, reaching across the aisle to work with Bliley and formulate a Food Quality Protection Act (Waxman and Green 2009). Both industry and environmentalists saw change as an improvement to the current system.

The bill Bliley and Waxman came up with was H.R. 1627, which would eventually pass. First though, it was turned over to two committees—the Subcommittee on Department Operations Nutrition, and Foreign Agriculture and the Subcommittee on Health and the Environment (U.S. Congress House 1995a; U.S. Congress House 1995b). Both held hearings on the bill and generated a report with recommendations from those hearings.

The first hearing, held by the Subcommittee on Department Operations, Nutrition, and Foreign Agriculture of the Committee on Agriculture, occurred on 16 May 1995 (U.S. Congress House 1995a). Ten out of thirteen witnesses at the hearing were industry representatives. Attendees included Jay Vroom, president of the American Crop

Protection Association, and Warren Stickle, of the Chemical Producers and Distributors Association. The other three attendees were Rebecca Doyle, from the Illinois Department of Agriculture, Lynn Goldman from the EPA, and Jay Feldman from the National Coalition Against the Misuse of Pesticides (U.S. Congress House 1995a).

In a meeting attended almost entirely by industry representatives, estrogenic chemicals and endocrine disruptors went almost entirely undiscussed (U.S. Congress House 1995a). At the hearing, only one attendee mentioned endocrine disruptors and pointed to the fact that the proposed Act contained nothing specifically addressing endocrine disruptors. Feldman, Executive Director of the National Coalition Against the Misuse of Pesticides, used his prepared statement to advocate for the need to address endocrine disrupting chemicals (U.S. Congress House 1995a, Prepared Statement of Jay Feldman). Feldman emphasized that endocrine disruptors particularly affect children and that their vulnerability should be dealt with by the new law. He referred to several familiar studies to make his point: declining sperm counts and rising rates of cancer. Feldman also emphasized wildlife studies to demonstrate the wider threat posed by endocrine disruptors, including Louis Guillette's work with alligators near super fund sites in Florida.

Endocrine disruptors made no other appearance at the hearing. There could be several reasons for that. First, the hearing was on the Food Quality Protection Act more broadly and industry representatives had other more important concerns for the Act that would regulate much of their business in the coming years. The proposed bill in no way mentioned endocrine disruptors or hormonally active chemicals and therefore would not prompt discussion of the topic. Second, the endocrine disruptor concept, which many in

the chemical industry referred to as "Colborn's hypothesis," was not popular with industry (Vogel 2012, 110). During the mid-1990s, they spent time and money publicly addressing the hormonal activity of their chemicals, downplaying its ability to cause negative effects, and funding studies showing the safety of their chemicals (Vogel 2012). Any regulation of endocrine disrupting chemicals would pose increased cost to chemical manufacturers, so it is no surprise that they did not bring up endocrine disruptors in the hearing. Ideas, trends, and fears that permeated previous hearings on chemical regulation were absent from the first hearing on the Food Quality Protection Act.

However, even given that, the Committee addressed endocrine disruptors in their final report (Committee on Agriculture 1996). In that report, the Committee commented they "[were] aware of recent scientific reports indicating that some pesticides may imitate, enhance, or block the activity of hormones in humans and wildlife," and asked that the EPA keep data on hormone disrupting pesticides (Committee on Agriculture 1996, 56). Proponents' work to integrate endocrine disruptors with the conversation about the Food Quality Protection Act clearly succeeded, even after a hearing where they played no role. The Committee did not recommend any changes to the bill specifically for endocrine disrupting chemicals, instead arguing that "the EPA … [had] sufficient authority to request information related to such effects [endocrine effects]" and to use that information in their approval process (Committee on Agriculture 1996, 56). But such a statement is an argument about executive branch authority rather than about the necessity of regulating endocrine disruptors. In essence, the Committee argued that the EPA should be taking endocrine disruptors into account, but that they did not need more authority from Congress to do it. By 1996, proponents had successfully convinced many

policymakers involved in regulating chemicals of the endocrine disruptor concept and category through linkage with big name diseases like breast cancer.

Hearing Before House Subcommittee on Health and Environment on the "Food Quality Protection Act," 1995

A month after the industry-dominated hearing took place, the Subcommittee on Health and Environment of the Committee on Commerce held a hearing on the "Food Quality Protection Act of 1995" (U.S. Congress House 1995b) The hearing was attended by a very different group. While several industry representatives testified, so too did representatives from several environmental groups like the NRDC and Citizens Action. Lynn Goldman and Mary Wolff both attended, as did Nancy Gould Chuda, the woman who first got Waxman interested in protecting children from pesticides (Waxman and Green 2009).

The final hearing brought back many of the patterns seen in previous hearings, namely the emphasis on breast cancer, children, and their connection to endocrine disruptors. Much of the testimony dealt with the fact that the proposed bill did not make special provisions to protect women from breast cancer. In particular, Wolff emphasized that strongly. In his questioning of her, Waxman revealed just how strongly breast cancer had been linked to endocrine disruptors, repeatedly using the catchall phrase "breast cancer and reproductive disorders" to refer to the effects of endocrine disruptors (U.S. Congress House 1995b).

That is revelatory of the work proponents successfully achieved with policymakers. During the hearings on chemical regulation in the US, proponents

advanced a narrow set of scientific studies that picked up on social fears and also helped to fill in the endocrine disruptor category. By the 1995 hearing, policymakers knew that endocrine disruptors caused breast cancer and reproductive disorders. Though many scientists still had serious questions about what counted as an endocrine disruptor and how to identify such chemicals, proponents had filled in the category enough for policymakers to know what endocrine disruptors do and why they should regulate them.

The report generated by the committee at the final hearing strongly recommended the addition of an estrogen substances screening program, a program run by the EPA "to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect" (Committee on Commerce 1996, 25). They amended Bliley's bill, H.R. 1627, to include such a provision before sending it back to the House in July (Committee on Commerce 1996). On 23 July 1996 at 1:32pm, Representative Pat Roberts motioned to suspend the rules and vote on the amended Food Quality Protection Act of 1996. The Act passed unanimously, with 417 votes in favor (Congressional Record House 1996). The next day, the Senate unanimously passed the bill (H.R. 1627 104th Cong.). Bill Clinton signed it into law on 3 August 1996 (H.R. 1627 104th Cong.).

Proponents Work Across Hearings to Achieve the Endocrine Disruptor Screening Program

Throughout the 1990s, proponents worked to solidify the endocrine disruptor category as a group of chemicals linked to politically powerful diseases in such a way that pushed for the regulation of those chemicals. In their testimony at hearings, as well

as their work with popular media, proponents used a specific group of studies to portray endocrine disruptors as a threat to the health of children, women, and men's reproductive organs. In doing so, they filled in necessary details of the endocrine disruptor category, but could not uncouple the connection between hormonally active chemicals and feminization, ultimately leading to legislation for an estrogenic substances screening program.

Across the hearings, proponents could largely control the endocrine disruptor narrative based on who was invited to testify. Witnesses at Congressional hearings have a fair amount of control over the information disseminated at the hearing, and therefore a fair amount of control over what science gets incorporated into regulation. No skeptics and few if any moderates on the endocrine disruptor concept attended any of the hearings. Individuals like Stephen Safe did not have the opportunity to present their scientific facts about endocrine disruptors, facts that called into question the linkage of endocrine disruptors with politically powerful diseases like breast cancer and undermined the solidity of the endocrine disruptor category proponents were trying to develop (Safe 1994; Safe 1995). Inclusion of those facts may well have led to very different regulatory conclusions. The attendance list at most of the hearings included environmental groups, Wingspread attendees, and breast cancer advocates, all of whom promoted the regulation of endocrine disruptors.[31]

[31] Industry groups worked against the concept, but were excluded from hearings more than once. They played a much larger role after the Endocrine Disruptor Screening Program was passed and parameters were being set by the EPA. Sarah Vogel details that extensively in her work *Is it Safe?* (Vogel 2012).

They did so by emphasizing endocrine disruptors and their connection to socially and politically powerful diseases and populations. At nearly every hearing, the same studies were referenced, the same facts given, the same story told. In particular, following the linkage of endocrine disruptors and breast cancer, the Wolff study dominated the hearings. In fact, at each hearing, the same studies or kinds of studies were mentioned each time: 1. Wolff's study linking breast cancer with exposure to DDT, 2. Nils E. Skakkebæk and Richard M. Sharpe's study linking estrogenic chemicals with sperm declines, and 3. A study linking *in utero* exposure to a chemical with developmental abnormalities in children (Wolff et al. 1993; Sharpe and Skakkebæk 1993; Jacobson, Jacobson, and Humphrey 1990; Jacobson and Jacobson 1996).

That collection of studies picks up almost exactly on the larger social concern about breast cancer and children, with the addition of Skakkebæk and Sharpe's study on sperm declines that seemed particularly horrifying to Congressmen. The repeated studies emphasized a certain view of endocrine disruptors, that they threatened women and children and should be regulated. By referencing those studies, proponents of the endocrine disruptor concept could take advantage of a particular kind of social capital generated by the fear of breast cancer and awareness of development. The studies also paralleled the emphasis laid by the same scientists in interviews with the media, meaning that the science in public spheres fed in to the science in regulatory spheres and vice versa. Hence, proponents really did take advantage of the tripartite nature of the concept to get endocrine disruptors regulated.

The studies proponents used also helped them clarify the endocrine disruptor category enough for policymakers. The category as proposed by researchers at

Wingspread in 1991 lacked specifics as to what chemicals counted as endocrine disruptors, how to identify endocrine disruption, and through what mechanisms endocrine disruptors function. Scientifically, that posed serious problems for the acceptance of the category and the concept throughout the 1990s, as discussed in Chapters 3 and 4. Socially, the broad strokes painted by proponents were enough to garner interest and drive fear of the new category, with few if any in the public pushing for a more fleshed out listing of endocrine disruptor characteristics. Within the regulatory sphere, proponents used their hearings to head off issues with the insubstantiality of the category by filling it with connections to breast cancer, sperm count declines, and effects in children. Proponents did not answer the question of most scientists at the time, of how a chemical would count as an endocrine disruptor. But they did solidify endocrine disruptor effects in their testimony and that drove the regulation of the substances.

That solidification was not without cost, however. The studies the proponents had to rely on to argue for the regulation of endocrine disruptors all highlighted the feminizing effects of estrogenic chemicals: increased rates of breast cancer, shrinking penises, sperm count declines. While the studies were politically and socially powerful, they created a lasting connection between estrogenic substances and the negative effects policymakers wanted to head off. That is apparent in the final language of the Food Quality Protection Act, which provides for an estrogenic substances screening program and makes no mention of endocrine disruptors anywhere. Without the work of Goldman and Browner, who had already introduced endocrine disruptor language at the EPA prior to passage of the Act, and the continued role of proponents in arguing for endocrine

disruptors at EPA meetings on how to implement regulation,[32] the US may not have ended up with the Endocrine Disruptor Screening Program.

CONCLUSION

In this chapter, I've laid out a two-part argument to explain how the Endocrine Disruptor Screening Program was passed and what role science played in the process. The 1990s were characterized by a unique set of circumstances that opened a window of opportunity for proponents of regulating endocrine disruptors. Those circumstances included the necessary end to a thirty-year-old regulatory clause and the welcoming Clinton administration that worked to regulate endocrine disruptors from within the EPA and Congressional hearings. It also included wider social engagement with the incidence of breast cancer and the awareness of development as a vulnerable time. Those four circumstances combined to increase the probability that endocrine disruptor regulation might pass by lowering barriers to its passage as well as increasing pressure to take action on the substances.

That opportunity, though, had to be capitalized on by the proponents of regulating endocrine disruptors. Those individuals—activist scientists, environmental groups, breast cancer advocates—used a narrow set of facts about endocrine disruptors in order to increase the sense that the substances needed to be regulated. By emphasizing the link between endocrine disruptors and breast cancer and endocrine disruptors and

[32] The work of proponents in the planning process after passage is documented thoroughly by Sarah Vogel in *Is it Safe?* (Vogel 2012).

development, proponents fit endocrine disruptors within a larger push to address those issues and took advantage of a kind of social capital that put pressure on legislators.

In that way, only very specific endocrine disruptor science got integrated into the regulation of endocrine disruptors. It was not a holistic understanding of the substances that led to their regulation. In fact, that may have led to the exact opposite. Instead, a specific kind of science was used to complete an agenda set by attendees at Wingspread, when they first defined the problem of endocrine disruptors: to regulate the substances.

The result of proponents' work was the single section in the Food Quality Protection Act calling for the establishment of a program to screen chemicals for estrogenic and other endocrine activity. Quickly after passage of the Act, the EPA convened the Endocrine Disruptor Screening and Testing Advisory Committee to determine the best methods to evaluate hormonally active pesticides. In 1998, the committee released its final report, urging the EPA to expand the testing of pesticides to commercial chemicals, environmental contaminants, cosmetics, polymers, and several other substances, as well as to include estrogen, androgen, and thyroid effects (EDSTAC 1998). Following the committee's report, the EPA spent close to a decade creating the initial list of chemicals to be tested and the tests that would be used to screen those chemicals.

In 2018, the Endocrine Disruptor Screening Program is a two-tiered screening program for possible endocrine disruptors. The company seeking approval for a new substance carries out all screening. The purpose of Tier 1 is to identify the chemical substance's interactions with estrogen, androgen, and thyroid screening pathways (Marty, 2014: 1). Tier 1 uses eleven chemical assays (five *in vitro* and six *in vivo*) to test that with

the goal of minimizing false negatives (though allowing for an increase in false positives) (Marty, 2014). Tier 2 aims to identify the adverse effects from the substance's interactions with the endocrine pathways identified in Tier 1 as well as to generate dose response data.

The Endocrine Disruptor Screening Program represents the totality of the US's attempts to regulate possible endocrine disruptors. Once a chemical has successfully made it through the program, companies are able to use the chemical with impunity. However, the program has received much scrutiny. Some of the scrutiny revolves around the cost of the program (Marty, 2014). More of the scrutiny, though, revolves around whether the program is effective at screening for endocrine activity and harm especially given the toxicological uniqueness of the chemicals in question.

As has been shown in this chapter as well as others in this dissertation, endocrine disruptors followed a unique regulatory path. Unlike many science policy issues, they did not start with broad scientific consensus, or even much scientific investigation. Instead, proponents set out from the beginning to direct social and regulatory attention to the chemicals and to push for their regulation in the face of deep scientific division. Their ability to successfully get endocrine disrupting chemicals regulated was the result of that tactic as well as the unique circumstances in the 1990s that allowed for large scale changes to the chemical regulations in the US. Given such criticisms of the Endocrine Disruptor Screening Program, it is worth thinking through whether the unique regulatory path taken by endocrine disruptors was the right path in terms of getting us to effective and useful regulations.

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CHAPTER 7

CONCLUSION

In this dissertation, I have laid out the life of the endocrine disruptor concept. The concept is a two-part idea originally proposed in 1991. Proponents of the concept first stipulate that some chemicals can interact and interfere with the normal functioning of hormones, resulting in negative health outcomes in humans and wildlife species exposed. Those chemicals are called endocrine disruptors and include the very common plasticizer bisphenol-A (BPA) as well as antimicrobials, pesticides, and many food packaging materials (Schug et al. 2016). The second part of the concept follows from the first, namely that endocrine disrupting chemicals, due to their potential to interfere with the health of organisms, pose a clear and immediate threat to human and wildlife populations. Throughout this work, I have emphasized that I am interested in the concept as a whole rather than the category of chemicals connected to it. That is because for much of the past thirty years, the concept and the category have been inseparable as a result of the way proponents introduced the concept in 1991, as discussed in Chapters 3 and 4.

In telling the biography of the endocrine disruptor concept, I have focused on one particular aspect: the construction of the concept as a scientific, social, and regulatory concern. Throughout these chapters, I have returned to the idea that when Theo Colborn and her colleagues proposed the concept in 1991, they explicitly and intentionally established it as a multifaceted object. That original group of twenty-one did not simply note that endocrine disruptors existed and should be investigated scientifically. They called for scientific investigation, social awareness, and regulatory action. Over the

course of the following years, members of that original group acted to ensure each of those goals, by speaking extensively in public media outlets like newspapers, by lobbying with policymakers and regulators to speak at hearings, and by publishing in scientific journals. The three-sided nature of the endocrine disruptor concept was a main driver throughout its life history, impacting its reception by the scientific community (Chapter 4), its study by that same community (Chapter 5), and its regulation by the US government (Chapter 6). The scientific, social, and regulatory aspects of the concept continue to drive the life of endocrine disruptors in the present day.

The historical moments covered in these chapters have very real implications for the modern day. When considering the endocrine disruptor concept in 2018, I am confronted by the deep disagreements between the scientists who study the chemicals, disagreements that originated in the 1990s. The varied interpretation of evidence of endocrine disruption that drove the animosity between Stephen Safe and Frederick vom Saal continues to drive the animosity between the new generation of endocrine disruptor scientists, many of them students of Safe and vom Saal. The persistent questions about the definition of endocrine disruptors and how to identify them lies at the heart of current discussions of how to regulate endocrine disruptors in the European Union (EU). The European Commission spent nine years attempting to establish a definition of endocrine disruptors to focus potential regulatory efforts (Paun 2018; European Commission 2018b). It failed. Regulations in the US also show the effects of the history laid out in this work. Modern efforts to improve testing mechanisms, shifting toward *in silico* models, have come up against the continued uncertainty about how endocrine disruptors disrupt as well as the persistent argument over what counts as a safe level of endocrine

disruption, wrapped up in new and old debates about low dose effects (EPA 2011a; EPA 2011b).

If there is one thing readers can take away from this dissertation, it's that how the endocrine disruptor concept was originally introduced had an outsize effect on how endocrine disruptors were studied, regulated, and talked about in 1991 and in 2018. The intentions and actions of activist scientists like Colborn to establish endocrine disruptors as objects of scientific social, and regulatory concern had profound impacts. I have laid out those impacts throughout this work and in doing so allow for reflection on whether the actions of Colborn and others and the regulatory, scientific, and social responses to those actions were appropriate. And what can be done in 2018 to move past them.

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