
Endocrine Disruptors: A Case Study on Atrazine

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I. INTRODUCTION

Endocrine Disrupting Chemicals (EDCs) represent a new type of human health and environmental risk that will challenge the current agency and regulatory system. Unlike carcinogens and other toxins, government agencies were not designed to regulate EDCs, which are much more complicated and difficult to understand. In order to illustrate these challenges, this paper will focus on the EDC atrazine.¹ Atrazine is the most widely used pesticide in the United States.² It is also relatively inexpensive and cost-effective as both an herbicide and a pesticide.³ Therefore, manufacturers have huge vested interests in proving that their number one selling herbicide, atrazine, is safe for both human beings and for the environment.⁴

Section II of this paper focuses on the history of atrazine as well as how its potential endocrine-disrupting properties came to light. Next, Section III explains why the properties of endocrine disruptors make scientific experimentation with atrazine complex. This explanation will be used to highlight the major obstacles in interpreting science in the field of endocrine disruption including: the setting of standard protocols, the complexities of animal studies, the difficulty of u-shaped

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¹ Atrazine (6-chloro-N-ethyl-N-isopropyl-1, 3, 5-triazine-2, 4-diamine) is the chemical name for the herbicide commonly known as triazine. ChemIndustry, Chemical Information Search, <http://www.chemindustry.com/chemicals/93825.html>.

² See Rex Dalton, *Doubts Linger over America's Top Herbicide*, 420 NATURE 256, 256 (Nov. 2002) (referencing atrazine as the "most widely used herbicide in the United States"); Tyrone Hayes et al., *Herbicides: Feminization of Male Frogs in the Wild*, 419 NATURE 895, 895-96 (Oct. 2002) [hereinafter Hayes, *Herbicides*] (calling atrazine the "most commonly used herbicide in the United States"); Tyrone B. Hayes et al., *Hermaphroditic, Demasculinized Frogs After Exposure to the Herbicide Atrazine at Low Ecologically Relevant Doses*, 99 NAT'L ACAD. OF SCI. PROC. 5476, 5476 (Apr. 2002) [hereinafter Hayes, *Hermaphroditic*] (calling atrazine "the most commonly used herbicide in the United States").

³ Syngenta Crop Protection, *Atrazine Valuable Production Tool for Farmers* (2003), <http://www.syngentacropprotection-us.com/prod/herbicide/atrazine/index.asp?> (follow "Atrazine's Value to Agriculture" hyperlink; then follow "Maximizing Economic Returns" hyperlink).

⁴ Major manufacturers include: Agan Chemical Manufacturing, LTD., Drexel Chemical Company, Oxon Italia S.P.A., Platte Chemical Company Inc., Sanachem LTD, and Syngenta Crop Protection Inc. Although many manufacturers engage in the production and sale of atrazine, this paper focuses on the manufacturer Syngenta.

dose response results, and the intense industry involvement. This section will also emphasize major differences between carcinogens and EDCs, which are important because most regulations were designed to control carcinogens. After discussing the practical and interpretational side of scientific evidence, Section IV examines the possible ways the current regulatory system could regulate an EDC. A focal point of this paper is to discuss the options available to the United States Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for regulating EDCs and how, in the case of atrazine, the EPA has chosen to exercise those options in light of the available evidence.

The paper will argue that the current environmental regulatory system is ill-prepared to deal with the complex toxic chemicals that are introduced by the modern chemical industry.

II. DISCOVERY OF ATRAZINE AS AN EDC

Atrazine has recently become a hot topic among scientists, policymakers, and manufacturers.⁵ However, atrazine's recent media attention is only the beginning of what has become a regulatory nightmare. As one of the first EDCs to be evaluated through the regulatory process,⁶ it is the perfect example of how unprepared regulators are to deal with these types of complex toxins. Researcher Tyrone Hayes' discovery of atrazine's endocrine-disrupting properties has led to the current media frenzy surrounding atrazine. Hayes' findings revealed that exposure to atrazine caused male frogs to become hermaphrodites.⁷ Specifically, the study showed that at low doses of atrazine, these deformed frogs had multiple sets of both male and female sexual organs.⁸

Given the widespread use and dependency of the American agricultural industry on atrazine, the implications of this study were shocking. In fact, atrazine is so widely applied that it is commonly found in the groundwater of states that use minimal amounts of the herbicide.⁹ For example, the United States Geological Society (USGS) reported atrazine levels in the groundwater of states, such as Utah, to be higher than the doses used in Hayes' laboratory experiments.¹⁰ Scientists have also reported the presence of atrazine in the European Alps.¹¹

Similar to the way in which Rachel Carson's book *Silent Springs*¹² created an

⁵ Marla Cone, *An Alarm Sounds for Amphibians*, L.A. TIMES, Jan. 25, 2006, available at <http://www.latimes.com/news/nationworld/nation/la-na-frogs25jan25,0,326876.story?coll=la-home-nation>; Environmental Protection Agency (EPA), Atrazine Chemical Registration, <http://www.epa.gov/oppsrrd1/reregistration/atrazine>.

⁶ See *infra* text accompanying notes 105-108; See generally EPA, Endocrine Disruptor Screening Program, <http://www.epa.gov/scipoly/ospendo/edspoverview/primer.htm> (discussing the relatively recent statutory authority to screen chemicals for their endocrine disrupting properties starting in 1996).

⁷ Hayes, *Herbicides*, *supra* note 2.

⁸ *Id.* (reporting studies on effects of atrazine pollution on *R. pipiens* larvae and wild leopard frogs).

⁹ *Id.* (stating that detectable amounts of atrazine were present within areas of non-agricultural states such as Utah, Wisconsin and Nebraska, with sales of atrazine below 0.4 kg km⁻²).

¹⁰ See Link TV Documentary, *Atrazine: Frogs, Farms and Pharmaceuticals* (Link TV Broadcast, Aug. 2004) (focusing on the recent controversies surrounding Syngenta, Dr. Ronald Kendall, the EcoRisk panel and Tyrone Hayes). The documentary also addressed how these controversies affect farmers and the general public. *Id.*

¹¹ *Id.*

¹² RACHEL CARSON, *SILENT SPRINGS* (Mariner Books 2002) (1962) (discussing the permeation of

acute awareness and focused public attention on unregulated chemicals in the environment, Hayes' study focused attention on the pervasiveness and potential toxicity of EDCs. With Hayes' research and the USGS findings, people suddenly became aware that EDCs could have frightening human health and environmental effects, were virtually everywhere and needed to be regulated.¹³

Hayes' original study was part of his research for Syngenta, one of the major manufacturers of atrazine. Upon Hayes' discovery, Syngenta carried out its own experiments through a panel of scientists called EcoRisk, which found Hayes' results to be faulty.¹⁴ However, according to the EPA's Scientific Advisory Committee after a nine-month evaluation, the subsequent Syngenta-funded studies were each flawed enough to be characterized as scientifically unsound.¹⁵

Many European countries have already banned the herbicide/pesticide atrazine. Fifteen European Union countries announced in October 2003 their decision to ban atrazine over the course of eighteen months.¹⁶ The recent bans of atrazine have put the EPA in quite a quandary.

III. DIFFICULT SCIENCE OF ENDOCRINE DISRUPTORS AND ATRAZINE

This section explores the many types of problems the EPA faces when interpreting science in this area, beginning with a background on endocrine disruption and atrazine. The analysis underscores the ways in which EDCs present new problems that the EPA has not had to address in the past when regulating carcinogens and other toxins.

chemicals into the environment). This book, first published in 1962, opened the eyes of the public to the problem of vastly unregulated use of pesticides that were leaching into the environment with unknown long-term consequences through the specific example of DDT. The public outcry instigated by this book led to the promulgations of environmental regulations like the banning of DDT and eventually FIFRA. See generally EPA, History of Pesticides and Public Health, <http://www.epa.gov/35thanniversary/publications/formative6.htm>.

¹³ See, e.g., Heloise Tarrant et al., *Endocrine Disrupting Substances in the Irish Aquatic Environment*, available at <http://www.epa.ie>; see EPA, Properties of EDCs, <http://www.epa.gov/ORD/NRMRL/EDC/basic.htm>; see, e.g., R. Tyler, S. Jobling, & J. P. Sumpter, *Endocrine Disruption in Wildlife: A Critical Review of the Evidence*, 28 CRITICAL REVIEWS IN TOXICOLOGY 319 (1998); Peter Matthiessen & Peter E. Gibbs, *Critical Appraisal of the Evidence for Tributyltin-mediated Endocrine Disruption in Mollusks*, 17 ENVTL. TOXICOLOGY & CHEMISTRY 37 (1998); DAVID E. KIME, ENDOCRINE DISRUPTION IN FISH (Kluwer Academic Publishers 1998).

¹⁴ Hayes, *Herbicides*, supra note 2. See Jennifer Lee, *Popular Pesticide Faulted for Frogs' Sexual Abnormalities*, N.Y. TIMES, June 19, 2003, at 20; Goldie Blumenstyk, *The Story of Syngenta and Tyrone Hayes at UC Berkeley: The Price of Research*, CHRON. HIGHER EDUC., Oct. 31, 2003, available at <http://www.mindfully.org/Pesticide/2003/Syngenta-Tyrone-Hayes31oct03.htm> (reporting on the details of Hayes' connection with Syngenta during his initial findings); Carl T. Hall, *From Boyhood Curiosity to Scientific Discovery: Biologist Tyrone Hayes Links Pesticides to Amphibian Deformities*, S.F. CHRON., Nov. 4, 2002, at A26, available at <http://www.mindfully.org/Pesticide/2003/Syngenta-Tyrone-Hayes31oct03.htm>; Bijal P. Trivedi, *Hermaphrodite Frogs Caused by Popular Weed Killer?*, NAT'L GEOGRAPHIC TODAY, Apr. 16, 2002, available at http://news.nationalgeographic.com/news/2002/04/0416_020416_TVfrog.html.

¹⁵ See Environmental Protection Agency (EPA), Scientific Advisory Panel (SAP), <http://www.epa.gov/scipoly/sap/2003/index.htm#061703> (providing schedule showing that the SAP met to discuss atrazine and the "potential developmental affects of atrazine on amphibians.") (last visited Dec. 5, 2005). The details and background of the Syngenta-funded research will be discussed *infra*.

¹⁶ Press Release, Natural Res. Def. Council (NRDC), EPA Refusal to Restrict Atrazine Despite Health Threat Ignores Scientific Evidence, says NRDC (Oct. 31, 2003) [hereinafter NRDC Atrazine Press Release], available at <http://www.nrdc.org/media/pressreleases/031031.asp>.

A. Endocrine Systems in General

To fully understand why the EPA was unprepared to regulate atrazine, lawmakers must understand exactly what it means for a toxin to be an EDC. As the name suggests, EDCs are toxic because they disrupt the normal function of the endocrine system.¹⁷ The endocrine system includes all hormone-secreting glands and regulates blood sugar, growth and function of reproductive systems, metabolism, development of the brain, and development of the nervous system.¹⁸ Most of these systems work on the principle of homeostasis or balance.¹⁹ Endocrine systems manage and regulate the amount of hormones in the body.²⁰ Endocrine systems have receptors that detect excess or inadequate amounts of hormones in the body and then react through a series of negative and positive feedback loops to keep the body in homeostasis.²¹ Endocrine systems can be found in most animals, not only mammals, including: fish, amphibians, reptiles, birds, snails, lobsters, and insects.²²

The basic endocrine system in all of these organisms is composed of hormones and their receptors.²³ These systems are so complex that they can be disrupted in a variety of ways. To analyze the possible channels of disruption, the EPA created the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) in 1996,²⁴ which focuses on identifying disruptors of estrogen, androgen and thyroid hormones.²⁵ EDSTAC has created four classifications for the testing and screening of suspected EDCs: (1) hold—chemicals not likely to interact with endocrine systems, (2) tier one screening—chemicals on which there is very little data in terms of their ability to disrupt endocrine systems, (3) tier two screening—chemicals about which the EPA has more information or for which the manufacturers have agreed to bypass tier one screening, and (4) hazard assessment—which includes dose response assessment.²⁶ Despite the creation of EDSTAC to specifically study these issues, EDSTAC only serves in an advisory capacity to the EPA and has no authority to

¹⁷See ENDOCRINE DISRUPTOR SCREENING AND TESTING ADVISORY COMMITTEE (EDSTAC) FINAL REPORT, CHAPTER TWO: BACKGROUND, 21-25 (Aug. 1998),

<http://www.epa.gov/scipoly/ospendo/docs/edstac/chap2v14.pdf> (discussing background information on the endocrine system and how it functions as part of EDSTAC's final report; EDSTAC is the Endocrine Disrupting Screening and Testing Advisory Committee created in 1996 to report directly to the EPA).

¹⁸ *Id.*

¹⁹ *Id.* at 21.

²⁰ *Id.*

²¹ *Id.*

²² EDSTAC FINAL REPORT, CHAPTER TWO: BACKGROUND, *supra* note 17, at 21.

²³ There are four classes of hormones: 1) steroids—derived from cholesterol; 2) amines—synthesized from amino acids; 3) peptides and proteins—consisting of chains of amino acids; 4) eicosanoids—made from arachidonic acid a 20-carbon fatty acid. There are also three classes of receptors: 1) receptors on cell surfaces to which peptide hormones bind, 2) receptors found in cell cytoplasm to which steroid hormones bind, 3) receptors in cell nuclei. *Id.*

²⁴ See EPA, Endocrine Disruptor Screening Program,

<http://www.epa.gov/scipoly/ospendo/edspoverview/edstac.htm> (stating that EDSTAC was formed in 1996) (last visited Dec. 1, 2005). See EDSTAC FINAL REPORT, CHAPTER TWO: BACKGROUND, *supra* note 17, at 21-25 (discussing the statutory authority for EDSTAC).

²⁵ These hormones can interfere with any of the following synthesis: release into blood stream, transport and serum binding, cell receptors, nuclear receptors, signal transduction, transcription, translation or metabolism. EPA, SAP, *supra* note 15, at 21-25.

²⁶ See Noah Sachs, *Blocked Pathways: Potential Legal Responses to Endocrine Disrupting Chemicals*, 24 COLUM. J. ENVTL. L. 289, 318-19 (1999) (discussing classifications under EDSTAC policy).

make final decisions. The information EDSTAC gathers goes into reports that are evaluated by the Scientific Advisory Panel (SAP).²⁷ Ultimately, in cases like atrazine, it seems that the SAP has more sway on EPA decisions than EDSTAC. EDSTAC has analyzed the data collectively and found that the present evidence regarding atrazine is not substantial enough to take concrete risk assessment-based actions.²⁸ From the EPA website, EDSTAC's position on atrazine and the status of its atrazine studies are unclear.

B. Specifics of Atrazine

As an endocrine disruptor, atrazine is thought to have both serious human health and ecological effects. The EPA's recent risk assessment states that the EPA suspects that endocrine disruptors may be responsible for adverse effects on the following bodily systems in humans: 1) female reproductive and development; 2) male reproductive; 3) hypothalamus and pituitary; 4) thyroid; and, 5) immunotoxicology.²⁹ Despite the EPA's suspicions, however, atrazine-specific human health studies have not been initiated. The EPA's risk assessment also states that atrazine is thought to have ecological effects because it can act as a phytoestrogen,³⁰ as demonstrated by representative examples in: invertebrates, fish, amphibians, reptiles, birds and mammals.³¹

Numerous scientific studies have demonstrated the potentially harmful properties of atrazine, such as its behavior as a phytoestrogen. When carrying out a risk assessment of atrazine, the EPA must look at these studies both individually and in

²⁷ See generally EPA, ENDOCRINE DISRUPTOR SCREENING AND TESTING ADVISORY COMMITTEE (EDSTAC) FINAL REPORT, CHAPTER ONE: INTRODUCTION, available at <http://www.epa.gov/scipoly/ospendo/edspoverview/edstac.htm>.

²⁸ Memorandum from Catherine Eiden, Senior Scientist, EPA, to Kimberly Love, Special Review Manager, EPA 63, (Apr. 16, 2002), available at http://www.epa.gov/oppsrrd1/reregistration/atrazine/hed_redchap_16apr02.PDF.

²⁹ See EPA RISK ASSESSMENT FORUM, SPECIAL REPORT ON ENVIRONMENTAL ENDOCRINE DISRUPTION: AN EFFECTS ASSESSMENT AND ANALYSIS 2-6 (Feb. 14, 2005) (1997), available at <http://www.epa.gov/ORD/WebPubs/endocrine/endocrine.pdf> (follow "E" hyperlink listed under "EPA Publications Source" then follow "Endocrine Disruption" hyperlink; then follow "Special Report on Environmental Endocrine Disruption: An Effects and Assessment Analysis" hyperlink; then follow "Special Report" hyperlink) (providing overview of current state of science for endocrine disruption).

³⁰ Phytoestrogens are substances that interfere with the endocrine system to produce more than normal amounts of estrogen. See Environmental Protection Agency (EPA), Endocrine Disruptors Research Initiative, www.epa.gov/endocrine; see also PBS Online Medical Glossary, <http://www.pbs.org/secondopinion/episodes/menopause/medicalglossary/story72.html>; The Free Dictionary's Medical Dictionary Page, <http://medical-dictionary.thefreedictionary.com/Phytoestrogens>; North Memorial Medical Center Online Health Encyclopedia, <http://www.northmemorial.com/healthencyclopedia/content/3166.asp>.

³¹ This occurs through a process called aromatase, which converts testosterone into estrogen. See Tyrone B. Hayes, Associate Professor of Integrative Biology, University of California, Berkeley, Richard G. Bond Memorial Lecture, Mayo Auditorium, University of Minnesota, How to Confuse the News: Industry Dilutes the Weight of Evidence in the Case for Atrazine as an Endocrine Disruptor (Feb. 26, 2004) (partial transcript), available at <http://ehs.umn.edu/files/hayesinfo.html> (proposing that atrazine induces aromatase in male amphibians); The Center for Regulatory Effectiveness, Atrazine.us: Environmental Impacts, <http://www.thecre.com/atrazine/environmentalimpacts.htm> (citing to and quoting from specific portions of the EPA's Environmental Risk Assessment in order to explain implications of aromatase in invertebrates and amphibians); Hayes, *Hermaphroditic*, *supra* note 2, at 5478 (discussing previous studies demonstrating that atrazine induces aromatase in mammals and reptiles).

the aggregate. When examining the scientific papers, the data on atrazine appears easily quantifiable and understandable; however, upon closer examination, the information lacks homogeneity. First, there are numerous testing methodologies.³² Even among the EPA's listed acceptable atrazine assays for thyroid function, for example, are several different methods, standards, and controls that could be used.³³ Additionally, different scientists use different statistical methods to analyze raw data. Thus, comparing the results of the various atrazine experiments in the same category, not to mention across categories, is difficult. Differences among the methodologies, standards, controls, and statistical analysis would not raise concerns if the studies came to the same conclusion; unfortunately, with the studies of atrazine, the results are incongruent.³⁴

C. Setting Standard Protocols and Analyzing the Results of Difficult Science

In addition to different methodologies, standards, controls and statistical analyses, the complexity of EDCs makes the scientific results difficult to compile and compare. In contrast, carcinogen testing data and experimentation, which the EPA has been dealing with over the past few decades, is much more consistent. Carcinogen tests are comparatively simple; for the most part, scientists simply count the number of malignant tumors present in the test subjects after they have been subjected to a certain dose of the carcinogen.³⁵ The consistent endpoint in carcinogen studies, i.e. the number of malignant tumors, makes the comparison of studies with different methodologies, standards, controls, and statistical analyses much easier.³⁶ For example, if study one uses methodology A to find four malignant tumors in each subject, while study two uses methodology B to find nine malignant tumors in each subject, it is relatively simple to go back and compare methodologies A and B to find likely reasons for this discrepancy. Similarly, scientists can develop experiment three relatively easily to resolve the discrepancy.

In the case of EDCs like atrazine, however, different endpoints make such comparisons exceedingly difficult.³⁷ In these studies, scientists cannot simply

³²See EPA, Endocrine Disruptor Screening Program, Assay Status Table, <http://www.epa.gov/scipoly/ospendo/assayvalidation/status.htm> (listing and describing many different assays).

³³ See EDSTAC FINAL REPORT, CHAPTER FIVE APPENDICES, APPENDIX K: BRIEF OVERVIEW OF ASSAYS CONSIDERED FOR TIER 1 SCREENING 28-34 (Aug. 1998) available at <http://www.epa.gov/scipoly/ospendo/docs/edstac/app-kv14.pdf>.

³⁴ *Id.*; Eiden, *supra* note 28.

³⁵ North American Control Animal Database Homepage, <http://www.epa.gov/ORD/NRMRL/EDC/basic.htm> (discussing the benefits of using uniform test subjects in experiments used to determine carcinogenicity given the normal methodology for carcinogenic testing in the scientific community); Harry A. MILLMAN & ELIZABETH K. WEISBURGER, HANDBOOK FOR CARCINOGEN TESTING SECOND EDITION (Noyes Publications, 1994); Donna Gulezian, David Jacobson-Kram, C. Bruce, McCullough, Harry Olson, Leslie Recio, Denise Robinson, Richard Storer, Raymond Tennant, Jerrold M. Ward & David A. Neumann, *Use of Transgenic Animals for Carcinogenicity Testing: Considerations and Implications for Risk Assessment*, 28(3) TOXICOL PATHOL. 428 (2000).

³⁶See, e.g., W.F. Lindsey, T.K. Das Gupta & C.W. Beattie, *Influence of the Estrous Cycle During Carcinogen Exposure on Nitrosomethylurea-Induced Rat Mammary Carcinoma*, 41 CANCER RES. 3857 (Oct. 1981).

³⁷ See, e.g., EPA, IMPLEMENTATION OF THE ENVIRONMENTAL PROTECTION AGENCY'S PEER REVIEW PROGRAM: AN SAB EVALUATION OF THREE REVIEWS A-5 (Sept. 2001),

compare four tumors to nine tumors; instead, they compare the number of additional sexual organs in experiment one to the number of instances of premature infertility in experiment two to the size of enlargement of organs in experiment three to stunted or hyperactive development in experiment four to abnormal behavior in experiment five.³⁸ These types of comparisons can be meaningless not just because of different methodologies, standards, controls and statistical analyses, but because of radically different endpoints, as well. These incompatible studies are a huge obstacle for the EPA. In the case of atrazine, studies have used a variety of different methods: exposing cells to atrazine, injecting test subjects with the substance, and feeding the subjects atrazine-contaminated food.³⁹ The studies have also used different reporting methods. Results of a study may state: the number of sexual organs, the size of organs, or the ability of the subjects to mature normally.⁴⁰ Thus, scientists have been asked to draw conclusions about atrazine based on experiments as disparate as the number of additional hermaphrodites among subjects living in atrazine-contaminated water and the effects on subjects directly injected with atrazine. Such a task is difficult, if not impossible, for both scientists in the field of toxicology and the policymakers making regulatory decisions based on the various conclusions.

The essential nature of the endocrine system and of endocrine disrupting chemicals (EDCs) complicates not only the science, but also the roles of regulatory agencies and policy makers because each of these endpoints can be deduced from a variety of processes. The study of toxicology is linked to the biological concept of homeostasis.⁴¹ The body is always trying to achieve a state of homeostasis, or balance, among all its different systems and chemicals. Each of these systems is regulated by the interrelationships of hormones, receptors, and chemical feedback loops. These systems are designed to keep the body in homeostasis whenever a new substance is added to the delicate dynamics that may throw the body off-balance.⁴² For example, if a subject eats large amounts of sugary foods, its blood sugar spikes, but the subject's endocrine system then uses negative feedback loops to bring the

<http://www.epa.gov/sab/pdf/rsac01009.pdf> (noting that peer review workgroup's interpretation depended on endpoints).

³⁸ See, e.g., Branimir Simiãc et al., *Effects of Atrazine on Reproductive Performance in the Rat*, 14(6) J. APPLIED TOXICOLOGY 401 (1994) (studying effects of atrazine on body weight, ovarian cycling, conception rate and size of litters of rats); Robert J. Kavlock, *Endocrine-Mediated Alterations on Development and Reproduction Following Exposure to Pesticides*, 24 J. TOXICOLOGICAL SCI. 265 (1999) (describing effect of atrazine on aging in female rats); C.A. Bishop et al., *Anuran Development, Density and Diversity in Relation to Agricultural Activity in the Holland River Watershed, Ontario, Canada (1990-1992)*, 57 ENVTL. MONITORING & ASSESSMENT 21 (1999) (linking existence of various pesticides, including atrazine, in rivers to egg hatching success and tadpole deformity of various species of toads and frogs); Suzanne E. Fenton et al., *Effects from Gestational Exposure to a Mixture of Atrazine and its Biological Metabolites in Male Long-Evans Rats*, 66 BIOL. REPROD. 199-200 (2002) (studying effects of atrazine on puberty, body weight, and endocrine and reproductive tract endpoints in male rats).

³⁹ See, e.g., Fenton et al., *supra* note 38 at 199-200 (using method of "gavage" (i.e. the introduction of nutritive material into the stomach by means of a tube) on pregnant rats).

⁴⁰ See, e.g., Simiãc et al., *supra* note 38 at 402-404 (analyzing differences in body weights, weights of other organs, successful mating rates, and litter sizes); Kavlock, *supra* note 38, at 265 (recording decreases in LH secretion from pituitary gland); Bishop et al., *supra* note 38, at 27-35 (studying differences in species densities, percentages of egg abnormalities, and percentages of tadpole deformities, and relating them to nutrient concentrations in the water).

⁴¹ See EDSTAC FINAL REPORT, CHAPTER TWO: BACKGROUND, *supra* note 17, at 21-25 (discussing background information on the endocrine system and how it functions).

⁴² *Id.*

blood sugar back into the normal range, back to homeostasis.⁴³

Each of the complex endocrine systems can be interrupted through a variety of mechanisms. For example, the body's regulation of the sex hormone androgen could be disrupted by: 1) a chemical that substitutes or acts like androgen and binds to androgen receptors; 2) a substance that inhibits or blocks androgen from binding to receptors; 3) a substance that breaks down androgen; or, 4) a chemical that combines with something else within the endocrine system that does one of the above, etc.⁴⁴ Disruption of the body's androgen regulation may then cause the body's regulation of other sex hormones (e.g. estrogen and testosterone) to be disrupted, as well.⁴⁵ Similarly, a certain result, like hermaphrodites among male frogs as in Hayes' experiment,⁴⁶ does not necessarily directly correlate with a specific, singular mechanism. This ambiguity makes the toxicologists' job difficult. Toxicologists must be able to pinpoint with certainty why exposure to a suspected EDC (i.e. atrazine) leads to certain endpoints (i.e. a sharp spike in the number of hermaphrodites).⁴⁷

This ambiguity in the study of atrazine starkly contrasts the certainty of results from exposing a test subject to a carcinogen and observing a greater number of malignant tumors. An experiment that can show a direct correlation between exposure to a particular substance and malignant tumors in a controlled laboratory environment leads to the conclusion that the substance is a carcinogen with minimal controversy. In contrast to atrazine and other suspected EDCs, DDT and asbestos have more directly and clearly related cause and adverse-effect relationships.⁴⁸ For example, exposure to asbestos has been proven to cause cancer.⁴⁹ Thus, scientists have established a clear one-to-one relationship between exposure to asbestos and cancer, which does not exist for EDCs.

D. Animal Studies: How many and which ones?

Experimentation with EDCs is being performed on a variety of organisms of different species, which adds another layer of complexity and difficulty to scientists' attempts to draw consistent conclusions. Atrazine experiments have been performed

⁴³ See Biology-Online.org, Physiological Homeostasis, Negative Feedback Control, http://www.biology-online.org/4/1_physiological_homeostasis.htm (last visited Dec. 1, 2005) (explaining homeostasis and the body's regulation of blood sugar).

⁴⁴ EDSTAC FINAL REPORT, CHAPTER TWO: BACKGROUND, *supra* note 17, at 21-25 (discussing background information on the endocrine system and how it functions).

⁴⁵ *Id.* at 24.

⁴⁶ Hayes, *Herbicides*, *supra* note 2.

⁴⁷ *Id.* at 895-96.

⁴⁸ See Press Release, EPA, New DDT Report Confirms Data Supporting 1972 Ban, Finds Situation Improving (Aug. 11, 1975), available at <http://www.epa.gov/history/topics/ddt/03.htm> (last visited Dec. 1, 2005) (discussing the general cancer and other toxic concerns surrounding DDT); EPA, Integrated Risk Information System, DDT (last visited Dec. 1, 2005) (using simple exposure and tumor count on rats to show DDT is carcinogenic), <http://www.epa.gov/iris/subst/0147.htm>; EPA, Superfund, Addressing Asbestos at Superfund Sites, <http://www.epa.gov/superfund/programs/asbestos> (last visited Dec. 1, 2005) (discussing the cancer risk assessment of asbestos).

⁴⁹ See Mesothelioma News, Mesothelioma Frequently Asked Questions, http://www.mesotheliomanews.com/faqs_whogets_mesothelioma.html (last visited Dec. 1, 2005) (describing that asbestos is the only known cause of mesothelioma).

with: mammals, birds, amphibians, reptiles, fish and invertebrates.⁵⁰ Undoubtedly, these dramatically different organisms have significantly different endocrine systems. Thus, the EPA is faced with questions, such as: how does one compare the results of atrazine exposure in a frog to those in a rat? In contrast, carcinogens and cancer experiments that study different species use the same indicator: the increase in the number of tumors.

Furthermore, sex hormones react differently in organisms of the same species at different stages of development, which is quite significant in studies of atrazine.⁵¹ Subjects' reactions to exposure—frogs in the case of the Hayes' experiment—may be dramatically different depending on their developmental stage; for example, exposure at the embryonic stage (eggs) may be vastly different from exposure at the adolescent stage (tadpoles), during puberty, as adults, or after menopause.⁵² Such differences in subjects' reactions occur with many carcinogens and toxins, including atrazine; however, because the endocrine system controls development and growth, the effect is magnified when dealing with the endocrine system.⁵³ Therefore, the results should be expected to vary more among populations at different developmental stages than with exposure to other carcinogens. The complexity and difficulty faced with atrazine studies are compounded because the cause-and-effect relationship is even farther removed where one cause can lead to a variety of results that differ from subject to subject. This inability to draw correlations between exposure and adverse effects will undoubtedly impact attempts to regulate EDCs, especially regarding the nation's most sensitive populations. For example, perhaps adults are not affected by exposure to atrazine, but those adults who were exposed to the substance at the embryonic stage will suffer huge developmental deformities or infertility.

Despite these difficulties in collecting and analyzing the impact of atrazine on organisms, this meta-analysis is crucial to reaching a robust scientific consensus on the properties of an EDC.⁵⁴ Still, the usefulness and persuasiveness of one type of experiment repeated several times and reaching the same result is limited when other types of experiments lead to opposite conclusions. Furthermore, the individual atrazine studies are, for the most part, wholly disconnected from each other because few of the experiments build on, or even reference, the data collected by other scientists.⁵⁵ Thus, a plethora of unrelated experiments on the effects of atrazine as

⁵⁰ EDSTAC FINAL REPORT, CHAPTER ONE: INTRODUCTION, *supra* note 27.

⁵¹ EPA Basic Informational Website, <http://www.epa.gov/ORD/NRMRL/EDC/basic.htm> (describing the properties of EDCs); EDSTAC FINAL REPORT, CHAPTER TWO: BACKGROUND, *supra* note 17.

⁵² Hayes, *Hermaphroditic*, *supra* note 2, at 5476 (showing different results when frogs are exposed to sex hormones at different developmental stages); A. Mantovani, A.V. Stazi, C. Macri, F. Maranghi & C. Ricciardi, *Problems in Testing and Risk Assessment of Endocrine Disrupting Chemicals with Regard to Developmental Toxicology*, 39(8) CHEMOSPHERE 1293 (Oct. 1999).

⁵³ EDSTAC FINAL REPORT, CHAPTER TWO: BACKGROUND, *supra* note 17, at 21-25 (discussing background information on the endocrine system and how it functions as part of EDSTAC's final report).

⁵⁴ See Hayes, *supra* note 31 (emphasizing the inadequacy of research already performed with amphibians and atrazine-induced aromatase).

⁵⁵ See, e.g., EPA: Data Evaluation Reports, *available at*

<http://www.epa.gov/scipoly/sap/2003/june/dataevaluationreportshtm.htm>, (listing a representative sampling of scientific papers researching the endocrine disrupting properties of atrazine), J. Shafer, Thomas R. Ward, Connie A. Meacham & Ralph L. Cooper, *Effects of the Chlorotriazine Herbicide*,

an endocrine disruptor exist, yet scientists have not aggregated the data or otherwise put the various studies together in a meaningful way.⁵⁶

Therefore, discord exists among the scientific research on atrazine for numerous reasons, including differing endpoints, subjects, methodologies, standards, controls and statistical analyses. Though the EPA created the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) in 1996 to resolve this problem and make sense of the evidence on atrazine and other EDCs, EDSTAC has not lived up to its potential.⁵⁷ While EDSTAC has made great strides by gathering the available studies together in one place and analyzing the data collectively, the Committee has concluded that the results are too inconclusive to take risk assessment-based actions.⁵⁸ Furthermore, EDSTAC has not fostered probing scientific research, such as more meta-analysis and studies that build upon previously published papers. By promoting research of this type, EDSTAC could expedite a clear scientific consensus to enable the EPA to make informed decisions about EDCs, like atrazine, and the possible need for their regulation.

E. U-shaped, Instead of Linear, Dose Response Curves

The problems for regulators go beyond the meta-analysis issues of endpoints, methodologies, animal studies, and the complexity of the endocrine system itself. Should the EPA decide to regulate atrazine, the Agency may find crafting the proper regulations difficult given the recent finding that most toxins, including EDCs, follow a U-shaped curve.⁵⁹ Therefore, toxicologists now believe that exposure to toxins at the extremes (i.e. very low and high levels) has more adverse effects on homeostasis than at mid-level exposure rates.⁶⁰ This is, in short, a regulating nightmare.

Cyanazine, on GABA_A Receptors in Cortical Tissue from Rat Brain, 57 TOXICOLOGY 142 (1999) (providing examples of disparate studies with endpoints that make comparison and meta-analysis difficult); Ralph L. Cooper, Tammy E. Stoker, Jerome M. Goldman, Michelle B. Parrish & Lee Tyret, *Effect of Atrazine on Ovarian Function in the Rat*, 257 REPROD. TOXICOLOGY 10 (1996). See generally Chapter 5 of EDSTAC Final Report, (discussing the difficulties of meta-analysis and setting up systematic assays for EDCs), available at

<http://www.epa.gov/scipoly/oscpendo/edspoverview/finalrpt.htm>. See also *id.* at Appendices J and N (attempting to set out the various papers that look at the different endpoints of routine experiments, or assays, that attempt to pinpoint properties and mechanisms for EDCs); *id.* at Appendices K-R (attempting to set out the possible mechanisms for testing for endocrine disrupting chemicals).

⁵⁶ *Id.*

⁵⁷ EPA, Endocrine Disruptor Screening Program, *supra* note 6.

⁵⁸ Noah Sachs, *Blocked Pathways: Potential Legal Responses to Endocrine Disrupting Chemicals*, 24 COLUM. J. ENVTL. L. 289 (1999); Eiden, *supra* note 28.

⁵⁹ See generally Edward J. Calabrese & Linda A. Baldwin, *Toxicology Rethinks Its Central Belief: Hormesis Demands a Reappraisal of the Way Risks are Assessed*, 421 NATURE 691 (Feb. 2003).

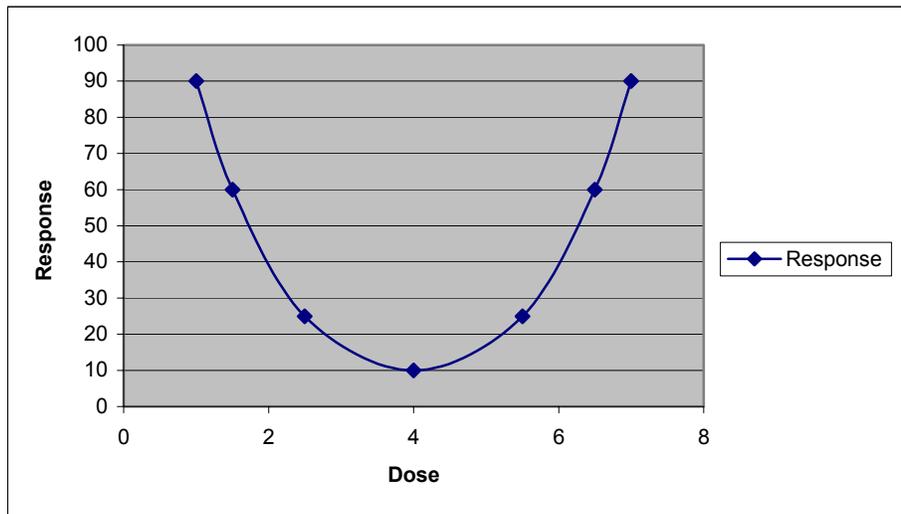
⁶⁰ See, e.g., Thomas Steeger & Joseph Tietge, *White Paper on Potential Developmental Effects of Atrazine on Amphibians* 54 (July 17, 2005) (submitted to FIFRA Scientific Advisory Panel, Washington, D.C., May 29, 2003),

available at <http://www.epa.gov/scipoly/sap/2003/june/finaljune2002telconfreport.pdf>; Sara I. Storrs & Joseph M. Kiesecker, *Survivorship Patterns of Larval Amphibians Exposed to Low Concentrations of Atrazine*, 112 ENVTL. HEALTH PERSP. 1056, 1057 (July 2004),

available at <http://ehp.niehs.nih.gov/members/2004/6821/6821.html>.

Raw Data⁶¹

| Dose | 1 | 1.5 | 2.5 | 4 | 5.5 | 6.5 | 7 |
|----------|----|-----|-----|----|-----|-----|----|
| Response | 90 | 60 | 25 | 10 | 24 | 60 | 90 |

U- Curve Relationship⁶²

How does the EPA regulate an EDC that has a U-curve effect? Regulation becomes tricky because the Agency knows causing levels of exposure to drop may, in fact, *increase* the health and environmental risks.⁶³ For example, excessive clean-up could be just as bad as, or worse than, over-exposure. Additionally, different individuals in different stages of development (i.e. individuals of different ages, body sizes, genders) may react dramatically differently at these higher and lower levels of exposure. These results can paralyze regulating agencies, like the EPA.⁶⁴ Unfortunately, as technology improves, toxicologists believe that exposure to most harmful substances will result in a U-shaped response curve.⁶⁵ Also, the discovery

⁶¹ Calabrese, *supra* note 59; Steeger, *supra* note 60; Noah Sachs, *Blocked Pathways: Potential Legal Responses to Endocrine Disrupting Chemicals*, 24 COLUM. J. ENVTL. L. 289, 316-19 (1999). This fictional data is merely for illustrative purposes.

⁶² *Id.*

⁶³ *Id.*; Charles W. Schmidt, National Institute of Environmental Health Sciences, The Lowdown on Low-Dose Endocrine Disruptors, Environmental Health Perspectives (EHP), <http://ehp.niehs.nih.gov/docs/2001/109-9/niehsnews.html> (discussing the inverted-U dose response curve that occurs at low doses of certain endocrine disrupting chemicals).

⁶⁴ See FIFRA SCIENTIFIC ADVISORY PANEL (SAP) REPORT, POTENTIAL DEVELOPMENTAL EFFECTS OF ATRAZINE ON AMPHIBIANS 3, 18-21, SAP Report No. 2003-01 (Aug. 4, 2003), available at <http://www.epa.gov/scipoly/sap/2003/june/junemeetingreport.pdf>.

⁶⁵ *Id.*

of exactly which intermediate levels of exposure pose the least risk may take years of research. Therefore, even if a consensus can be reached as to whether atrazine poses human health and environmental threats, the question of how and in what manner it should be regulated may remain a difficult, if not impossible, question to answer.

F. Pattern of Industry Interference: A Brief History of the Tobacco Industry's Suppression of Damaging Scientific Information

The problems discussed so far are either unique to EDCs or of special concern to the study of EDCs; however, industry involvement is an issue that impacts the entire environmental regulation arena. Manufacturers have always had a vested interest in showing that their products are safe and should not be regulated⁶⁶; in cases where the science is already difficult to interpret, industry may find it irresistible to interfere. In the case of atrazine, industry-funded EcoRisk studies seem to intentionally create doubt about the validity of studies showing atrazine to be an EDC.

The notion of industry-funded scientists using illegitimate science to deceive regulators into believing that legitimate studies are faulty is remarkably similar to similar actions by the tobacco industry regarding studies showing increases in cancer from second hand smoke exposure.⁶⁷ For years the tobacco industry funded both studies "disproving" the link between smoking and lung cancer and the work of scientists who "muddied the waters" by arguing that studies establishing a link between smoking and cancer were scientifically flawed.⁶⁸ The tobacco industry's studies were so successful that regulators and policymakers did not believe there was sufficient scientific evidence connecting smoking and cancer,⁶⁹ which delayed action against the tobacco industry by almost a decade after the first publications of studies showing the link.⁷⁰

The tobacco industry's reaction to the Takeshi Hirayama study is a prime example of the industry's manipulation of information.⁷¹ Hirayama's study was published in 1981 by the *British Medical Journal* and demonstrated a link between second hand smoke and lung cancer.⁷² The study followed over 90,000 non-smoking Japanese

⁶⁶ Wendy E. Wagner, *The Precautionary Principle and Chemical Regulation in the U.S.*, 6 (3) HUMAN & ECOLOGICAL RISK ASSESSMENT 459 (May-June 2000) (discussing how manufacturers have an incentive to be ignorant about adverse affects of their products as it reduces liability and the concern for close regulation); James O'Reily & Amy Dalal, *Off-Label or out of Bounds - Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 309 (2003).

⁶⁷ See, e.g., American Cancer Society Condemns Tobacco Industry Study for Inaccurate Use of Data: Study Part of Organized Effort to Confuse Public about Secondhand Smoke (May 15, 2003), http://www.cancer.org/docroot/MED/content/MED_2_1x_American_Cancer_Society_Condemns_Tobacco_Industry_Study_for_Inaccurate_Use_of_Data.asp; see *infra*. pp. 17-22.

⁶⁸ See generally Thomas O. McGarity, *On the Prospect of "Daubertizing" Judicial Review of Risk Assessment*, 66 LAW & CONTEMP. PROBS. 155 (2003); see also Monique E. Muggli, Richard D. Hurt & D. Douglas Blanke, *Science for Hire: A Tobacco Industry Strategy to Influence Public Opinion on Second Hand Smoke*, 5 (3) NICOTINE & TOBACCO RESEARCH 303 (June 2003); Jonathan M. Samet, M.D., M.S. & Thomas A. Burke, *Turning Science Into Junk: The Tobacco Industry and Passive Smoking*, 91(11) AM. J. PUB. HEALTH 1742 (Nov. 2001).

⁶⁹ McGarity, *supra* note 68.

⁷⁰ *Id.*

⁷¹ *Id.*

⁷² See Takeshi Hirayama, *Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer: A*

housewives over a fourteen-year period.⁷³ The results showed a marked increase of incidence of lung cancer among women married to smokers as opposed to non-smokers.⁷⁴ Soon after the Hirayama study was published, the Trichopoulos study affirmed the connection between second hand smoke and lung cancer.⁷⁵

The tobacco industry used a variety of tactics to undermine the validity of these studies. First, the industry encouraged scientists on their payroll to comment on any potential ways to undermine the adverse results. Almost immediately, industry consultants like Theodore D. Sterling published letters in the *British Medical Journal* claiming that Hirayama's methodology had not adequately controlled for differences between urban and rural settings.⁷⁶ Hirayama responded by arguing that he had controlled for economic and social class and that he had found higher incidences of smoking among males of higher socio-economic class.⁷⁷ However, Hirayama also found no noticeable difference in the incidences of cancer among those who used kerosene stoves or were exposed to other indoor air pollutants.⁷⁸ Hirayama was more than willing to consider confounding factors, but had not found any hard evidence of such factors in his study.⁷⁹ Sterling, however, steadfastly held on to the theory of confounding factors for many years despite the lack of any evidence.⁸⁰

Second, the tobacco industry launched a campaign to undermine the statistical methods used in the Hirayama study. Hirayama had used the "Mantel-extension chi test" to evaluate the raw data in his study.⁸¹ After a discussion with industry consultants and statisticians, Tobacco Institute Representative, Dr. Kastenbaum, came to believe that the study contained a "fundamental error" in its use of the Mantel-extension chi test.⁸² He argued that, if corrected for the error, the numbers published in Hirayama's study would prove to be wrong and, hence, that there was no statistically significant link between second hand smoke and lung cancer.⁸³ Dr. Mantel, creator of the Mantel-chi-test, stated that he would "entertain the possibility that Hirayama had made a critical mistake," but further detailed analysis would be necessary.⁸⁴ An analysis of the original, unpublished data would have to be evaluated to conclude whether a mistake had been made. The industry did not wait. On June 10, 1981, the Tobacco Institute announced through a press release that Professor Tsokas and Dr. Mantel had "confirmed the existence of a fundamental

Study from Japan, 282 BRIT. MED. J. 183 (1981).

⁷³ *Id.*

⁷⁴ *Id.* See also McGarity, *supra* note 68, at 158 (asserting that epidemiological studies are the most effective method for hazard assessment after "human tests" or controlled experiments, which are often not possible for ethical reasons).

⁷⁵ See Dimitrios Trichopoulos et al., *Lung Cancer and Passive Smoking*, 27 INT'L J. CANCER 1 (1981).

⁷⁶ McGarity, *supra* note 68, at 181.

⁷⁷ *Id.*

⁷⁸ *Id.*

⁷⁹ *Id.*

⁸⁰ *Id.*

⁸¹ Steeger, *supra* note 60.

⁸² McGarity, *supra* note 68, at 181.

⁸³ *Id.*

⁸⁴ McGarity, *supra* note 68, at 190.

mathematical error.”⁸⁵ Tobacco industry statisticians and consultants, like Peter Lee, warned that careful analysis suggested that Hirayama had not made a statistical error and that Dr. Mantel had only suggested the possibility of error and not stated definitively that such an error had been made.⁸⁶ Instead of heeding the warnings and calling off the media blitz against Hirayama’s work, the tobacco industry tried to keep Lee quiet, calling in other experts to counter Lee’s calculations first by claiming that Lee had not done the calculations, and then simply by calling his calculations faulty.⁸⁷

At this point, the General Council for the British American Tobacco Company advised Lee not to go public with his statements to preserve his reputation.⁸⁸ Several years later, German tobacco industry scientist Franz Adlkofer openly stated that, “Hirayama was correct, TI [Tobacco Institute] knew it . . . [The] TI published its statement about Hirayama knowing that the work was correct.”⁸⁹ Consequently, because of the delay in the affirmation of the studies, the EPA did not carry out a draft risk assessment (DRA) and make it available for public view and comment based on these studies until 1990, almost ten years after the Hirayama study.⁹⁰

G. Tobacco Again?

Is history repeating itself? Dr. Hayes was employed by Syngenta when he made his initial discoveries connecting atrazine and EDC.⁹¹ His employment contract with Syngenta prohibited him from publishing his results; therefore, only after Hayes left and was no longer bound by his contractual confidentiality agreement was he able to publish his study in *Nature*.⁹² In response, Syngenta and other pesticide/herbicide manufacturers created a panel of scientists, called EcoRisk, which included Dr. Ronald Kendall, Ph.D., to conduct research on atrazine as an EDC.⁹³ When Hayes’ results were finally published, Syngenta used the EcoRisk studies to discredit his findings.⁹⁴ The EPA’s Scientific Advisory Panel (SAP) examined each and every one of the studies conducted by EcoRisk and found every study fundamentally flawed for numerous reasons, including starving test subjects and mingling control and test subjects by leaving tanks open.⁹⁵ It is difficult not to suspect foul play.

⁸⁵ *Id.* (quoting News Release from the Tobacco Institute for Immediate Use Accompanied by Text of Cablegram to Japan and Memorandum from Dr. Mantel 1 (June 10, 1981) (Bates No. 500651585)).

⁸⁶ *Id.* at 191.

⁸⁷ *Id.* at 191-93.

⁸⁸ *Id.*

⁸⁹ McGarity, *supra* note 68, at 191-93 (quoting Memo from J. Wells to E. Pepples, *Re: Smoking and Health-Tim Finnegan*, July 24, 1981).

⁹⁰ EPA, RESPIRATORY HEALTH EFFECTS OF PASSIVE SMOKING: LUNG CANCER AND OTHER DISORDERS xvi (Dec. 1992), available at http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36793.

⁹¹ See Trivedi, *supra* note 14 (reporting that Hayes left Syngenta in November of 2002 to pursue his work independently).

⁹² Goldie Blumenstyk, *The Price of Research: A Berkeley Scientist Says a Corporate Sponsor Tried to Bury His Unwelcome Findings and Then Buy His Silence*, 50 THE CHRON. OF HIGHER EDUC. A26 (Oct. 2003), available at <http://chronicle.com/free/v50/i10/10a02601.htm>.

⁹³ Link TV Documentary, *supra* note 10.

⁹⁴ *Id.*

⁹⁵ POTENTIAL DEVELOPMENTAL EFFECTS OF ATRAZINE ON AMPHIBIANS, *supra* note 64, at 16-17; Link TV Documentary, *supra* note 10.

The facts surrounding the Hayes-Syngenta controversy beg the question: are the scientists on the EcoRisk panel deliberately creating scientifically unfounded studies to refute Hayes' study in the same way that tobacco industry scientists deliberately tried to undermine the statistically-sound Hirayama study? These are legitimate questions. The SAP, part of a government agency unencumbered by the demands of the private industry, found every single EcoRisk panel study fundamentally flawed, which certainly suggests that foul play is a strong possibility.⁹⁶

If the tobacco industry could easily manipulate science in studies where the link between lung cancer and second-hand smoke was direct, the implications of industry interference in the case of more complex toxins like atrazine and other EDCs is extremely disconcerting. The statistical methods used to study the cancer-smoking link are relatively simple and better established compared to those for EDCs. For example, to study the cancer-smoking link, simply expose the subject and then wait to see how many tumors develop, or compare the exposed population to the unexposed population and examine the differences in the number of cancers.⁹⁷ This method cannot be applied to the study of EDCs.⁹⁸ Finding populations exposed to and not exposed to a particular EDC *and* populations that are similar enough in socio-economic status and environment that a comparison would be free of confounding factors, is both difficult and costly.⁹⁹

The fact that low-level exposure to EDCs cause multiple sexual organs to develop in some animals should raise grave concerns. A direct, simple pathway between a particular EDC and its effect may never be discerned, in contrast to the strong connection between smoking and lung cancer. Each EDC, just like with atrazine, can have myriad effects and each of those effects can be caused by a variety of other factors.

IV. HOW TO REGULATE

Given the problems associated with the scientific analysis of the toxins, a careful examination of the regulations available to the EPA is imperative. Also, by drawing attention to the currently available regulatory options, this section will use the case study of atrazine to underscore the ways in which the EPA has used the regulations.

A. FIFRA: Help or Hindrance?

Once the available data has been interpreted, the EPA and other regulators have a limited number of options. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) is the federal statute under which pesticides and herbicides, like atrazine, are supposed to be regulated.¹⁰⁰ EDCs could also be regulated under the Toxic

⁹⁶ POTENTIAL DEVELOPMENTAL EFFECTS OF ATRAZINE ON AMPHIBIANS, *supra* note 64, at 16-17.

⁹⁷ *See supra* note 37.

⁹⁸ *See generally* EDSTAC Final Report, Chapter 5, *available at*,

<http://www.epa.gov/scipoly/oscpoverview/edspoverview/finalrpt.htm> (describing the difficulties of setting up systematic assays for EDCs); *see also id.* at Appendices J and N (attempting to set out the various papers that look at the different endpoints of routine experiments, or assays, that attempt to pinpoint properties and mechanisms for EDCs); *id.* at Appendices K-R (attempting to set out the possible mechanisms for testing for endocrine disrupting chemicals); *infra.* at pp. 12-15.

⁹⁹ *Id.*; McGarity, *supra* note 68, at 181.

¹⁰⁰ Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C.A. §§ 136 – 136y (West 2005).

Substances Control Act (TSCA),¹⁰¹ the Endangered Species Act (ESA),¹⁰² the Safe Drinking Water Act (SDWA),¹⁰³ the Clean Air Act (CAA),¹⁰⁴ the Clean Water Act (CWA),¹⁰⁵ and the Food and Drug Administration (FDA),¹⁰⁶ depending on the use and properties of the specific EDC. The following discussion will be limited to FIFRA because it is most relevant to the atrazine case.

Under FIFRA are two categories of chemicals, those that are already in use and those that manufacturers will be introducing into the market.¹⁰⁷ Chemicals that are new to the market are subjected to higher standards than those already in use.¹⁰⁸ When FIFRA was enacted, this different standard probably stemmed from practical necessity, i.e. to “grandfather in” certain age-old pesticides and herbicides. However, subjecting some substances to lower regulatory standards could lead to problematic results. Newer, safer products that are potentially viable substitutes for older substances composed of suspected EDCs, may be subjected to more scrutiny and consequently may not be readily approved.

Putting this problem aside for the moment, consider that atrazine was recently subjected to the registration review process under FIFRA¹⁰⁹ as a pesticide that is already in use, but subject to periodic review.¹¹⁰ Clearly, from FIFRA § 138(c)(A), the burden of proof in the registration process lies with the registrant or manufacturer.¹¹¹ In the case of atrazine, this includes companies like Syngenta. During the review process, the EPA could have taken a wide variety of regulatory approaches with atrazine, if the Agency had determined that atrazine posed an unreasonable risk to the environment.¹¹² The EPA could have: (1) banned atrazine; (2) classified atrazine as a restricted use pesticide under §136(d)(2) or §136(d)(3)¹¹³; (3) modified the labeling, instructions, and warnings required for atrazine; (4) limited the sales to reserve stocks; (5) suspended sales of atrazine; or (6) simply renewed the current registration on the basis that there is no sound data that atrazine is an EDC.

EPA faced a difficult decision, given the complicated scientific obstacles. What is an “unreasonable” environmental risk? Is it enough that atrazine is a suspected EDC? Knowledge that atrazine is an EDC is probably not enough to prove a human health risk, but is probably more than enough to show an unreasonable environmental risk exists regardless of what type of organism atrazine affects.

¹⁰¹ 15 U.S.C. §§ 2601-2692 (2000).

¹⁰² 16 U.S.C. §§ 1531-1544 (2000).

¹⁰³ 42 U.S.C. §§ 300-300(f) (2000).

¹⁰⁴ 42 U.S.C. §§ 7401-7671 (2000).

¹⁰⁵ 33 U.S.C. §§ 1281a-1294 (2000).

¹⁰⁶ 21 U.S.C. § 393 (2000).

¹⁰⁷ FIFRA, 7 U.S.C. § 136 (2000).

¹⁰⁸ *Id.*

¹⁰⁹ FIFRA, 7 U.S.C.A. § 136(g)(A) (West 2005).

¹¹⁰ EPA, Pesticides: Topical & Chemical Fact Sheets, Atrazine Interim Registration Eligibility Decision (IREDD) Q&As – Jan. 2003, <http://www.epa.gov/pesticides/factsheets/atrazine.htm>; 7 U.S.C. § 136g(a)(1)(A).

¹¹¹ FIFRA, 7 U.S.C. § 138c(a) (2000).

¹¹² FIFRA, 7 U.S.C. § 136d(b)(2) (2000).

¹¹³ *Id.*

FIFRA only requires a showing of “environmental risk,”¹¹⁴ but other statutes which may govern suspected EDCs that are not pesticides, herbicides, or fungicides require the higher burden of “human health risk.”¹¹⁵ Determining if something is an unreasonable risk is complicated by the U-curve dose response phenomenon that is quickly becoming dominant in the field of toxicology.

If the EPA decides that atrazine presents an unreasonable environmental risk, the best way to regulate the substance is unclear. If the mechanism is unknown then it is uncertain whether all, or just some, uses are unsafe. First, the EPA must address this lack of concrete information. Section 136(c)(2)(B) allows the EPA to carry out a “Data-call-in,” meaning the EPA can tell the manufacturer exactly what information to provide and then give the manufacturer a reasonable amount of time to produce that information.¹¹⁶ Again, the burden is on the manufacturer, which is efficient since the manufacturer has the best resources and access to information about the herbicide/pesticide. Therefore, the manufacturer is in the best position to carry out experiments and analyze data. Conversely, the manufacturer also has the strongest economic incentive to present biased results. Independent laboratories and researchers not funded by industry have no vested interest in the outcome of their studies and, therefore, are the most likely to be impartial, especially when they have an incentive to maintain a reputation for providing unbiased results.¹¹⁷ Perhaps, however, industry will withhold information and independent researchers will be given less than full access to the industry’s data and resources.

B. Summary of Atrazine’s Re-registration Under FIFRA

Unfortunately, despite all of these available options, a regulatory agency like the EPA may conclude that the toxicity of a substance is too controversial to be regulated without stronger evidence. This is a problem in the field of endocrine disruption because these toxins are so complicated that clear, uncontroversial evidence may take decades to produce.¹¹⁸ The EPA’s regulatory difficulties are best illustrated with the EcoRisk panel results discussed *supra*.¹¹⁹ Syngenta decided not

¹¹⁴ FIFRA, 7 U.S.C. § 136(bb) (2000).

¹¹⁵ See, e.g. Toxic Substances Control Act (TSCA), 15 U.S.C. § 2601(1976); Federal Food, Drug and Cosmetic Act (FFDCA), Delaney Clause 21 U.S.C. § 409 (1958); Safe Drinking Water Act (SDWA) 43 U.S.C. § 300(f) et. seq. (1974); Occupational Safety and Health Act (OSHA) 29 U.S.C. 61 et seq. (1970); Food Quality Protection Act (FQPA) P.L. 104-170; 110 Stat. 1489 (amended FIFRA and FFDCA) (1996); Federal Water Pollution Control Act Amendments of 1972 (FWPCA) PL 92-500 (1972); Endangered Species Act (ESA) 7 U.S.C. § 136; 16 U.S.C. § 460 (1973); Emergency Planning and Community Right-to-Know Act (EPCRA) 42 U.S.C. § 11011 et seq. (Title III of Superfund Amendments Reauthorization Act of 1986—SARA) (1986); Clean Water Act 33 U.S.C. § 1251 et seq. (1977); Clean Air Act (CAA) 42 U.S.C. § 7401 et seq. (1970).

¹¹⁶ FIFRA, 7 U.S.C. § 136a(c)(2)(B) (2000).

¹¹⁷ James Robert Brown, *Essays on Science and Society: Privatizing the University—the New Tragedy of the Commons*, 290 SCI. 1701-1702 (2000); Joel Lexchin, Lisa A Bero, Benjamin Djulbegovic & Otavio Clark, *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 BRIT. MED J. 1176 (2003); Mohit Bhandari, Jason W. Busse, Dianne Jackowski, Victor M. Montori, Holger Schünemann, Sheila Sprague, Derek Mears, Emil H. Schemitsch, Dianne Heels-Ansdell & P.J. Devereaux, *Association Between Industry Funding and Statistically Significant Pro-Industry Findings in Medical and Surgical Randomized Trials*, 170 (4) CAN. MED. ASSOC. J. 481-83 (2004).

¹¹⁸ *Infra*. pp. 4-23.

¹¹⁹ See also Link TV Documentary, *supra* note 10.

to go public with the Hayes study,¹²⁰ and instead opted to carry out more atrazine experiments through EcoRisk.¹²¹ Hayes went public with his study,¹²² and EcoRisk quickly responded with more studies showing an opposing outcome.¹²³ Hayes claims that he independently recreated the results of his original experiment fifty-one times.¹²⁴ EcoRisk has countered Hayes' studies with studies of its own.¹²⁵

At first, the Syngenta-funded studies were thought to provide direct evidence disproving Hayes' original findings, just as in the tobacco cases. Now, however, connections between the scientists, the source of funding, and regulators have cast serious doubts on the reliability of these studies.¹²⁶ Both the EPA and the National Resources Defense Council (NRDC) asked that the Interim Registration Eligibility Decision (IREED) deadline for atrazine required by FIFRA be extended from August 3, 2002 to July 31, 2003 so that they could consider the EcoRisk studies in light of what had become a media controversy.¹²⁷ The EPA's Scientific Advisory Panel (SAP) discussed and reported its findings in a meeting that took place July 17-20, 2003.¹²⁸ The Chair of the EcoRisk panel, Dr. Ronald Kendall, Ph.D., also served as the head of the EPA's SAP one year before EcoRisk testified before it.¹²⁹ The fact that Dr. Kendall was not asked to recuse himself from the proceedings for ethical conflict of interest reasons is suspect.¹³⁰

As previously stated, Syngenta funded the EcoRisk research panel to study the possibility that atrazine was an EDC.¹³¹ The results of these studies overwhelmingly demonstrated that Hayes' original experiment was incorrect and that atrazine was not

¹²⁰ Hayes, *Herbicides*, *supra* note 2.

¹²¹ See Lee, *supra* note 14; Rebecca Renner, *Controversy Clouds Atrazine Studies*, ENVTL. SCI. & TECH, Feb. 19, 2004, available at http://pubs.acs.org/subscribe/journals/esthag-w/2004/feb/science/tr_controversy.html;

Link TV Documentary, *supra* note 10 (focusing on the recent controversies surrounding Syngenta, Dr. Ronald Kendall, the EcoRisk panel and Tyrone Hayes). The documentary also focuses on how these controversies affect farmers as well as the general public. *Id.*

¹²² Hayes, *Herbicides*, *supra* note 2; see also Tyrone B. Hayes, *There is No Denying This: Defusing the Confusion About Atrazine*, 54 BIOSCIENCE 1138, 1138-49 (Dec. 2004).

¹²³ See Lee, *supra* note 14; Renner, *supra* note 121; Link TV Documentary, *supra* note 10; Kerry Tremain, *Hopping Mad: A Frog Biologist Battles an Agrichemical Giant*, SIERRA MAG., July/Aug. 2004, available at <http://www.sierraclub.org/sierra/200407/profile.asp>; Web page maintained by Assoc. Prof. Paul Z. Myers, Biology Dept., Univ. of Minn.,

http://scienceblogs.com/pharyngula/2006/02/tyrone_hayes_at_umm.php#more.

¹²⁴ Link TV Documentary, *supra* note 10.

¹²⁵ See Lee, *supra* note 14; Renner, *supra* note 121; Link TV Documentary, *supra* note 10; Tremain, *supra* note 123; Myers, *supra* note 123.

¹²⁶ See, e.g., Natural Resources Defense Council, EPA Won't Restrict Toxic Herbicide Atrazine Despite Health Threat—White House documents obtained by NRDC reveal that industry influenced the decision, Jan. 23, 2004, <http://www.nrdc.org/health/pesticides/natrazine.asp>.

¹²⁷ See EPA, Office of Pesticide Programs, Atrazine Evaluation Deadline Extension, available at http://www.epa.gov/oppfead1/cb/csb_page/updates/atrazinext.htm.

¹²⁸ EPA, SAP, Schedule of Meetings & Agendas, <http://www.epa.gov/scipoly/sap/2003/index.htm>.

¹²⁹ Link TV Documentary, *supra* note 10 (focusing on the recent controversies surrounding Syngenta, Dr. Ronald Kendall, the Eco Risk panel and Tyrone Hayes, and how these controversies affect farmers and the general public).

¹³⁰ *Id.*

¹³¹ See Lee, *supra* note 14; Renner, *supra* note 121; Link TV Documentary, *supra* note 10; Myers, *supra* note 123; Tremain, *supra* note 123.

an EDC.¹³² It took the SAP nine months to completely analyze the data presented in these studies.¹³³ The results were that every single one of the Syngenta studies was found to be either: (1) methodologically flawed, (2) statistically flawed, or (3) in some way fundamentally biased.¹³⁴ Flaws included problems as basic as neglect and starvation of the test subjects.¹³⁵ Given these results from the EcoRisk panel, agencies and policy makers should be extremely cautious about accepting the results of industry-funded research at face value.¹³⁶ In summary, the SAP concluded that each of the EcoRisk studies was flawed or biased so that it could not contribute to the scientific debate surrounding atrazine in a meaningful way.¹³⁷

The case of atrazine and the controversy surrounding Syngenta, Dr. Kendall, and Dr. Hayes illustrate how the analysis of the discord among scientists becomes complicated when money and political issues enter the picture. How reliable are studies funded by those with vested interests like Syngenta and other manufacturers?

In addition, wasted resources are a serious concern. The nine months that the SAP spent evaluating these studies spent resources that might have been better used elsewhere instead of debunking the results of faulty research.¹³⁸ Time and effort could have been directed towards analyzing the results of independent researchers, designing experiments to build on established findings, or engaging in meta-analysis of existing evidence. Policymakers must seek more efficient ways to get better information.

On October 31, 2003, the EPA finalized the IRED, allowing atrazine to be approved because the Agency determined that, even though the SAP discredited the Syngenta studies, evidence was insufficient to prove that atrazine was a risk to human health or the environment.¹³⁹ The Agency's move implies that the perceived uncertainty around atrazine and the lack of meta-analysis has created a situation where a regulatory feels powerless against private industry. In contrast, on October 15, 2003, European Union Nations announced that they would ban atrazine, which implies that European Union countries have a regulatory system erring on the side of caution when dealing with complex toxins.¹⁴⁰

C. Accusations

The 2003 IRED is not the end of the atrazine story. The Natural Resources Defense Counsel (NRDC) has filed lawsuits against both the White House and the

¹³² See Lee, *supra* note 14; Renner, *supra* note 121 (stating EcoRisk “planned, funded, and executed the atrazine studies criticized by Hayes”); Link TV Documentary, *supra* note 10; Myers, *supra* note 123; Tremain, *supra* note 123.

¹³³ See EPA, SAP, *supra* note 15 (showing dates SAP met to discuss atrazine).

¹³⁴ See POTENTIAL DEVELOPMENTAL EFFECTS OF ATRAZINE ON AMPHIBIANS, *supra* note 64, at 16-17 (discussing flaws in studies thereby limiting their scientific usefulness).

¹³⁵ *Id.*

¹³⁶ See Link TV Documentary, *supra* note 10 (focusing on the recent controversies surrounding Syngenta, Dr. Ronald Kendall, the EcoRisk panel and Tyrone Hayes).

¹³⁷ Link TV Documentary, *supra* note 10.

¹³⁸ See EPA, SAP, *supra* note 15 (showing dates SAP met to discuss atrazine); Atrazine Evaluation Deadline Extension, *supra* note 127.

¹³⁹ See NRDC Atrazine Press Release, *supra* note 16 (discussing the EPA's conclusions in light of SAP findings).

¹⁴⁰ *Id.*

EPA.¹⁴¹ In November 2003, the NRDC brought the lawsuits for withholding documents and blocking the NRDC's investigation into the role the chemical industry played in the EPA's atrazine decision.¹⁴² The NRDC claims that "industry" (Syngenta and other manufacturers of atrazine) and the White House played inappropriate roles in shaping the EPA's decision not to place limitations on atrazine.¹⁴³ The EPA, according to NRDC reports, struck a private deal with the manufacturers of atrazine that included: an agreement that the EPA would not regulate atrazine and that Syngenta would, in return, perform a small number of tests on the effects of atrazine on frogs; an agreement that Syngenta would monitor forty of the 1,172 watersheds identified by the EPA as being at high-risk for atrazine pollution (3.4%) and the EPA would take no steps to protect those left unmonitored; and a determination by the EPA that Syngenta would be required to take additional steps only if the monitoring of 3.4% of the high-risk watersheds showed persistent contamination levels of above ten to twenty ppb, including further monitoring, possible introduction of buffer zones, and use of other "application methods" for the most contaminated of the forty streams monitored by Syngenta.¹⁴⁴

Furthermore, the EPA contends that the burdens placed on Syngenta and other atrazine manufacturers in the chemical's re-registration process are consistent with the recommendations of the independent SAP that met for three days to review the EPA's assessment of available atrazine studies.¹⁴⁵ The monitoring standards described in the agreement between the EPA and Syngenta derive from the system of Maximum Containment Levels (MCLs) established under the Safe Drinking Water Act (SDWA).¹⁴⁶ Whether the risk of atrazine as an EDC had any effect on the setting of the MCL for that chemical or whether the MCL is based purely on the level of toxicity necessary to cause cancer is unclear.

Additionally, the NRDC filed suit against the EPA in August of 2003 for failing to carry out its obligations under the Endangered Species Act (ESA).¹⁴⁷ The NRDC claims that the EPA ignored its legal obligations under the ESA when the Agency decided not to place limits on atrazine despite its own scientific conclusions that existing levels of atrazine could jeopardize endangered species populations.¹⁴⁸ The EPA, according to the NRDC, failed to communicate with the Fish and Wildlife Service and the National Marine Fisheries Service regarding atrazine's risks to endangered species.¹⁴⁹ In effect, the NRDC is attempting to use the ESA to regulate

¹⁴¹ See Press Release, Natural Resources Defense Council, NRDC Sues EPA for Failing to Protect Endangered Wildlife from Herbicide (Aug. 20, 2003), <http://www.nrdc.org/media/pressreleases/030820.asp> (discussing basis of NRDC's lawsuit against the EPA).

¹⁴² *Id.*

¹⁴³ *Id.* (stating that the government concedes to the industry's demands, regardless of the threat to public health).

¹⁴⁴ NRDC Atrazine Press Release, *supra* note 16.

¹⁴⁵ EPA, Pesticides: Topical & Chemical Fact Sheets, Atrazine Interim Registration Eligibility Decision (IRED) addendum Q&A's (Oct. 2003), http://www.epa.gov/pesticides/factsheets/atrazine_addendum.htm.

¹⁴⁶ *Id.*

¹⁴⁷ NRDC Atrazine Press Release, *supra* note 16.

¹⁴⁸ *Id.*

¹⁴⁹ *Id.*

EDCs, even though the Act was not legislated for that purpose.¹⁵⁰

As the NRDC attempts to interpret the available scientific evidence in a way that meets the evidentiary standards necessary to justify regulation, the NRDC will likely encounter the same problems that confronted the EPA. The NRDC will have to consider the complexities of EDCs, the muddled science involved in evaluating them, and the numerous studies examining them, each having its own methodology, endpoints and varying species at different stages of development. Even if clear evidence of atrazine's risk to human health and the environment had existed, the U-shaped dose response curve still would have resulted in an uncertain response by EPA. Syngenta, on its official website, states that the company has agreed to follow the EPA's advice and carry out appropriate testing to determine the possible effects of atrazine.¹⁵¹ The EPA's official policy is not to comment on pending litigation.

Clearly, FIFRA is not the only statute under which EDCs can be regulated, though atrazine clearly falls under FIFRA regulations. Any attempts at regulation using science-based regulatory standards to analyze EDCs will result in the same issues and problems as those that the EPA has encountered under FIFRA. In addition to regulation under FIFRA, the ESA, and the SDWA, EDCs could also be regulated under the TSCA, the CAA, the CWA, and the FDA.

D. Public Response

The more complicated the issues become, the more the public is confused. Is atrazine bad? Was it all a false scare? Who is telling the truth? Is the EPA downplaying the risk or is the NRDC exaggerating it? There are no simple answers to these questions, and the average citizen quickly loses interest in convoluted topics. This is extremely problematic in relation to chemical regulation issues because often in such situations public pressure is necessary to pressure agencies to make difficult decisions. Atrazine is cheap, cost-effective, and has no comparable substitutes, so farmers have a strong economic incentive to use it for as long as possible. Economically rational farmers will continue to experience economic gain while farm workers and the general public suffer the costs of atrazine use. This results in a classic environmental justice problem.

V. CONCLUSION

Whether or not atrazine is ultimately determined to be an EDC, policymakers and agencies have a lot of catching up to do in order to deal with the toxicology implications of new and complex chemicals. In the future, more chemicals will be discovered or created that act like EDCs, and attempts to regulate them will give rise to the same issues discussed here. The techniques and tactics used to deal with carcinogens will be inadequate. The government should be more proactive, spend more of its resources encouraging independent research in areas of concern by offering grants, organizing conferences, raising awareness, and keeping a closer eye on new advances in toxicology. There are no quick and easy solutions to these

¹⁵⁰ See U.S. Fish and Wildlife Service, Findings, Purposes, and Policy of The Endangered Species Act of 1973, <http://www.fws.gov/endangered/esa.html>.

¹⁵¹ Sherry Ford, Science Panel Supports EPA Views on Atrazine/Amphibian Research, Syngenta Crop Protection (Aug. 7, 2003), <http://www.syngentacropprotection-us.com/prod/herbicide/atrazine/>.

obvious, but complex problems. Awareness of the systemic issues is a good start, but each obstacle must be addressed individually with respect to each chemical in need of regulation. Scientific research on atrazine will continue. It remains to be seen if regulations and regulatory institutions will change to adapt to this new type of toxin.