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No Observed Adverse Effects: Developing Neurons, Organophosphate Insecticides, and the 1996 Food Quality Protection Act

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A Note on Format:

The format of this thesis subscribes to the conventions of historical research rather than to the conventions of basic science research. The thesis therefore follows the following format:

Introduction: Establishes the study's purpose, context, and background.

Main Body: Presents historical findings, integrating data and analysis to clarify the issues presented and to begin to build a particular argument.

Conclusion: Synthesizes the analysis to offer a succinct interpretation of the events and a further explanation of the importance of the issues explored.

Abstract

"NO OBSERVED ADVERSE EFFECTS:" DEVELOPING NEURONS, ORGANO-PHOSPHATE INSECTICIDES AND THE 1996 FOOD QUALITY PROTECTION ACT. Brendan R. Jackson (Sponsored by John Harley Warner). Department of the History of Medicine, Yale University School of Medicine, New Haven, CT.

Physicians are familiar with organophosphates (OPs) as a classic, though obscure, cause of cholinergic poisoning. Many opportunities for human exposure exist—sixty million pounds of OPs are applied as insecticides to sixty million acres of U.S. land each year, and, until recently, over one-fifth of Americans used these chemicals in their homes. Most physicians, however, still know little about the dangers that these pesticides pose to the developing nervous system. By the late 1980s, toxicologists increasingly recognized that toxicants such as lead and mercury, even at doses well-below the level required to cause symptomatic poisoning, could induce subtle, yet permanent, neurological deficits if the exposure occurred during critical periods of brain development. In the early 1990s, scientists and regulators began to realize that developmental neurotoxicity (DNT), as this phenomenon was called, could also result from OPs. In 1996 Congress passed the Food Quality Protection Act (FQPA), marking a major turning point in the regulation of hazardous chemicals. Prior to the FQPA, the Environmental Protection Agency (EPA) based its calculations of pesticide risk on adults and largely neglected the increased susceptibility of infants and children. The new law took a precautionary stance, protecting the vulnerable neural and physical development of the fetus and child with the inclusion of a 10-X safety factor, and shifting the burden of proof from health advocates to the pesticide manufacturers. The ensuing ten-year battle between health groups, pesticide manufacturers, and the EPA over the law's enforcement now provides an instructive lesson into the complex scientific, political, and economic world of environmental health, and serves as a relatively successful example of effective policy improving public health.

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Abbreviations and Glossary

ACPA	American Crop Protection Association (now CropLife America)
AFBF	American Farm Bureau Federation
CU	Consumer's Union
CDC	Centers for Disease Control and Prevention
CRA	Cumulative Risk Assessment
DFP	Diisopropyl Fluorophosphate
DNT	Developmental Neurotoxicity
EPA	Environmental Protection Agency
EWG	Environmental Working Group
FDA	Food and Drug Administration
FQPA	Food Quality Protection Act of 1996
IPM	Integrated Pest Management
LOAEL	Lowest Observed (or Observable) Adverse Effects Level
NAS	National Academy of Sciences
NIEHS	National Institute of Environmental Health Sciences
NOAEL	No Observed (or Observable) Adverse Effects Level
NRC	National Research Council (the research arm of the NAS)
NRDC	Natural Resources Defense Council
OP	Organophosphate
OC	Organochlorine (including DDT, dieldrin, and chlordane)
OPIDP	Organophosphate-Induced Delayed Polyneuropathy
TOCP	Tri-Ortho-Cresyl Phosphate (a non-pesticide OP causing OPIDP)
USDA	United States Department of Agriculture

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Introduction

> *So much literature dealing with the adverse effects of pesticides on human and animal life has appeared in the years since the 1962 publication of Rachel Carson's* Silent Spring *that the author of yet another work on the subject feels obligated to provide an apology.*
>
> -*James Whorton,* Before Silent Spring, *1974* [1]

Pesticide. It has been a word full of undertones for over a hundred years. To the mid-twentieth-century American public, it connoted sanitation and hygiene, freedom from mosquito-borne disease and from pestilence itself. To many in the post-*Silent Spring* era, it conjures images of a skull and cross bones, environmental destruction, and health hazards. For farmers it has meant less worry and more profitable crops, and for consumers, more plentiful and appealing fruits and vegetables. Over one billion pounds of pesticides are applied in the United States annually, now nearly 4 pounds per person. Their economic impact is enormous, and their health effects incompletely known. One must begin any history of pesticides with the knowledge that its subject contains a loaded word, which elicits strong reactions on all sides.

The health concerns about pesticides have changed with the varying compounds and uses, and also with the state of scientific understanding. Initial worries generally regarded the immediate and poisonous effects of pesticides, and only later did concerns about chronic pesticide exposure arise. Essential to this changing focus were improved quantitative methods that allowed researchers and regulators to measure human pesticide exposure at levels below previous limits of detection. Additionally, advancing epidemiological and animal studies revealed pesticides' more subtle health effects. In

this paper I focus on an instructive yet contentious example of this transition in a group of insecticides commonly known as the organophosphates (OPs). Acute neurological poisoning from OPs has long been recognized; still, only since the mid-1980s have investigators seriously examined the long-term effects of OPs on brain development. Expanding evidence caused many scientists to suspect early-life exposure to even low levels of some organophosphates created subtle, but permanent, nervous system deficits. This phenomenon, known as developmental neurotoxicity (DNT), became a key issue in the understanding and regulation of not only insecticides, but also chemicals in general.

The recent history of organophosphates, particularly regarding developmental neurotoxicity, includes a landmark epistemological shift within the realm of chemical regulation and our understanding of risk. This transition came in the form of the 1996 Food Quality Protection Act (FQPA), which mandated that the Environmental Protection Agency (EPA) change the way it examined pesticides' health risks. Former standards specified a risk/benefit calculation in which a pesticide's health risks were to be balanced against its economic benefits. The EPA operated under a familiar toxicology assumption that if studies showed no conclusive evidence of toxicity, no toxicity existed. This idea stood in contrast to the general principles of medicine and public health, fields devoted to preventing or forestalling adverse health consequences even in the face of uncertain evidence. Beginning in the 1980s, environmental health specialists began pushing for the application of a "precautionary principle" for pesticides and later played a major role in shaping the FQPA. The clearest evidence of the precautionary principle at work in the FQPA is the incorporation of a ten-fold safety factor for pesticide tolerances (the level of acceptable pesticide residue remaining in food). This safety factor, included to protect

infants and children, could only be removed if “reliable data” demonstrated a lower margin of safety for this age group [2]. Congress, armed with a reasonable suspicion of pesticide’s harm to children and acknowledging that standards based on current studies were inadequate, voted to act in a surprisingly precautionary manner. This breakthrough legislation turned traditional risk assessment on its head by mandating a reduction in pesticide exposure and forcing industry to prove that higher exposures were safe. It also removed the prior risk/benefit paradigm and instead based regulatory decisions solely on health [2]. Finally, the inclusion of the safety factor, partially aimed toward developmental toxicities, effectively reversed pesticides’ risk calculus and reignited the fierce debate about the role of science in pesticide regulation.

Though the environmental, entomological, industrial, governmental, and medical literature on insecticides is enormous, and though their early history is well studied, health historians offer little attention to developments since 1980. *Silent Spring*’s publication in 1962 produced a minor flurry of historical interest in the ensuing decades. For example, in 1975 James Whorton wrote *Before Silent Spring*, which covers the history of pesticides from antiquity to the introduction of DDT and particularly concentrates on the early-twentieth-century [1]. Thomas Dunlap’s *DDT: Scientists, Citizens, and Public Policy*, published in 1981, provides a detailed history of this famous and infamous pesticide [3]. *Silent Spring*’s popularity afforded health historians the opportunity to write about the history of pesticides for a broader audience, yet historical accounts diminish after the 1980s.

Recent scholarship on organophosphates includes historian Linda Nash’s 2004 article “The Fruits of Ill-Health: Pesticides and Worker’s Bodies in Post-World War II

California," [4] and a 2006 book on California agriculture and health, *Inescapable Ecologies* [5]. Edmund Russell's 2001 book, *War and Nature: Fighting Humans and Insects with Chemicals from World War I to Silent Spring*, illustrates the German and American military role in the development of organophosphates and other insecticides, as well as the martial marketing techniques used by manufacturers [6]. While the above works examine pesticides' environmental destructiveness and acute health effects, little historical attention has been given to their chronic health consequences. The most comprehensive narrative on this subject was written not by an historian, but by a professor of environmental policy, John Wargo. In 1996 Wargo wrote *Our Children's Toxic Legacy: How Science and Law Fail to Protect Us from Pesticides*, which offers an introduction to adverse health risks from chronic pesticide exposure as well as an overview of recent pesticide policy and regulation [7].

In this paper I aspire to contribute to the historical understanding of pesticides and health. Particular attention is warranted on the less studied chronic and non-cancer effects of pesticides, perhaps best highlighted through the case study of organophosphates and developmental neurotoxicity. The timeframe examined is necessarily broad, given that organophosphate use spans over sixty years and associated chronic adverse effects from such use span over forty; nonetheless, I confine much of the scientific and policy study to the decade following the enactment of the Food Quality Protection Act (FQPA) in 1996. There are two key events in the recent history of organophosphate regulation: the 1993 publication of the National Academy of Sciences' report *Pesticides in the Diet of Infants and Children*, and the 1996 legislation of the FQPA [2, 8]. The NAS report first raised public consciousness about the possible dangers of OPs to children from

developmental neurotoxicity, while the FQPA was the first significant law regarding pesticides in half a century.

I concentrate particularly on the past decade because it remains relatively unexamined from a historical perspective and because the implementation of the FQPA posed unique regulatory and public health questions. These questions, as I will explore, marked a profound change in the scientific and medical exploration of environmental toxins. As evidenced by the alphabet soup of government abbreviations in the above paragraph, this study focuses on the recent controversy in the United States, rather than a wider international scope, for American decisions on pesticide regulation carry widespread influence throughout much of the world. In doing so I intend to exemplify a particular application of the precautionary principle, rather than perform a comparative analysis.

Even from the limited perspective offered in this paper, the recent history of organophosphates is complex and somewhat daunting. Their numbers alone are impressive. Each year about sixty million pounds of OPs are applied to roughly sixty million acres of land in the United States [9]. Thousands of researchers across the country dedicate themselves to the study of these pesticides' myriad effects, and hundreds of employees of the Environmental Protection Agency (EPA) crunch numbers to inform regulatory decisions. Millions of farmers, homeowners, and exterminators use these insecticides daily, and billions of people worldwide experience benefits and harms from their use. Economically, the pesticide industry alone generates $11 billion per year [10]. In the United States, entrenched forces on all sides of the pesticide debate compete for greater influence over pesticide regulation. Industry groups like CropLife America

(formerly the American Crop Protection Association, and before that the National Agricultural Chemicals Association) [11] and the American Farm Bureau Federation (AFBF) [12] compete with environmental and public health groups like the Environmental Working Group (EWG) and the Natural Resources Defense Council (NRDC) in the bureaucratic, legal, and public relations arenas.

The actors above are not those traditionally seen in medical history. Furthermore, one sees few physicians, no patients, not even disease. Yet all parties have a significant impact on individuals' health, albeit on a subclinical level. The history of environmental health takes place largely outside the clinic and away from the hospital, and its historical documentation has only recently begun. The story of developmental neurotoxicity from organophosphate pesticides is instructive into the nature of environmental health history, and its sheer diversity of actors underscores the broad nature of environmental health itself.

In addition to the EPA, more traditional actors are involved in the pesticide story as well. The National Institute of Environmental Health Sciences (NIEHS), one of 27 branches of the National Institute of Health (NIH), performs independent research and distributes research funding to toxicologists and environmental health scientists at medical and public health schools across the country. NIEHS maintains an open-access research journal called *Environmental Health Perspectives*, where much of the recent health literature on organophosphates can be found. Furthermore, state programs, especially California's Department of Pesticide Regulation, are the source of many new initiatives on pesticides. These interest groups are considerably aided by physician participation in nearly all of them.

Historians Gregg Mitman, Michelle Murphy, and Christopher Sellers, in their introduction to the 2004 edition of the journal *Osiris*, entitled *Landscapes of Exposure*, argue that "it will become increasingly difficult to write the history of modern public health without asking many more questions about environment, ecology, and place" [13]. Recent works, including David Rosner and Gerald Markowitz's *Deceit and Denial: The Deadly Politics of Industrial Pollution* [14], Christopher Sellers's *Hazards of the Job: From Industrial Disease to Environmental Health Sciences* [15], and Sheldon Krimsky's *The Scientific and Social Origins of the Environmental Endocrine Hypothesis* focus on some of the environmental determinants of health. Robert Gottlieb's *Forcing the Spring: The Transformation of the American Environmental Movement* [16] and sociologist Robert Bullard's *Dumping in Dixie: Race, Class, and Environmental Quality* [17] address the role health has played in the environmental movement. Though I address the organophosphates from a medical, public health, and policy perspective, their story is inherently environmental as well. OP-induced illness is caused by external environmental factors, and the levels of exposure depend on the complex mixture of people, pesticides, and their environment.

The toxicology of organophosphates has become increasingly relevant. Public concern about the environment and chemicals, particularly pesticides, continues to grow. This is evidenced by the expanding market for organic food and "green chemistry," as well as the proliferation of groups claiming environmental causes for diseases such as autism, asthma, cancer, and infertility. As scientists and citizens acquire greater sophistication about the risks of synthetic chemicals, so must historians, even amateur ones. Here I will depict the growing complexity of the scientific evidence, regulation,

and debate surrounding OPs and place into perspective the expanding concerns for pesticides' low-level effects. I hope, in a larger sense, to play a role in the movement reconnecting our understanding of health to our place in the natural world.

Comprehensive background sections are included to highlight the role of environmental health in medicine and to provide context for a relatively unfamiliar topic to many in the historical field. These sections consist of the phenomenon of developmental neurotoxicity, including a brief case-study of lead poisoning; the organophosphates' place in the history of insecticides; and the early history of OPs. The main body of analysis occurs in the more recent sections, which deal with the origins of the FQPA, the initial reaction to its implementation, and the lasting effects and controversies.

Developmental Toxicology of Organophosphates

You too can be a toxicologist in two easy lessons, each of ten years.
-Arnold J. Lehman (circa 1955), Chief Toxicologist at the FDA [18]

The organophosphates comprise a group of more than thirty insecticides that are some of the most widely used in the world. They are also considered the most toxic to humans. Like all chemical insecticides, the OPs function by attacking insects' nervous systems [19]. In the same way organophosphates are toxic to insects, inhibiting the breakdown of the neurotransmitter acetylcholine, they are also neurotoxic to humans. In 1932 German chemist Willy Lange and his graduate student, Gerde von Krueger, first described symptoms of acute organophosphate exposure, noting "a feeling of pressure to the larynx and difficulty breathing," followed by a "disturbance in consciousness" and "blurred vision" [20]. In the ensuing decades, scientists have so thoroughly elucidated the

mechanism and effects of OPs that medical schools now use them as classic examples of nervous system dysfunction when teaching pharmacology and neurology. Yet according to the editors of a comprehensive textbook on organophosphate toxicology published in 2006, "although the literature on OP... insecticides is seemingly exhaustive and systematic, this is not the case" [20]. Private industry, whose data remain outside the public domain, has carried out much of the research on OPs. Furthermore, these authors identify a glaring omission in the body of research: nearly all toxicology testing has been on adult organisms; very few studies focus on children and developing animals.

During the 1980s many pediatricians, toxicologists, and environmental health scientists developed concerns about whether standard toxicology tests, used in determining the allowable exposure levels set by the Environmental Protection Agency, were adequate enough to protect children's health. Research in the 1970s and early 1980s on childhood lead poisoning showed that older studies and guidelines had underestimated children's special risk and sensitivity to lead. This raised the question—might children have heightened susceptibility to other chemicals, particularly to known toxicants like pesticides? In 1988 Congress requested that the National Academy of Sciences (NAS) appoint a committee to review the topic of children's exposure to pesticides. The final report, entitled *Pesticides in the Diet of Infants and Children*, published in 1993, outlined a number of deficiencies in the regulation and testing of pesticides. Among other issues the committee expressed "concern about the vulnerability of the developing human brain to any neurotoxic pesticides" [8]. Their concern stemmed from a rich field of research on lead, mercury, radiation, alcohol, and polychlorinated biphenyls (PCBs), which suggested that early life exposure to environmental toxicants,

even at low doses, could cause permanent brain damage by interfering with the brain's complex formation and maturation [21]. This phenomenon, called "developmental neurotoxicity," would, in the 1990s, change the debate over organophosphates. With further study, doses that toxicologists once thought harmless were regarded with suspicion due to deleterious effects on developing fetuses and children. The standard pediatric dictum, "children are not little adults," acquired new meaning regarding pesticides [8].

The field of toxicology has its own dictum: "the dose makes the poison," derived from the father of toxicology, Theophrastus Bombastus von Hohenheim (1493-1541), better known as Paracelsus. In the sixteenth century he wrote "Alle Ding sind Gift und nichts ohn Gift; alein die Dosis macht das ein Ding kein Gift ist [All substances are poisons; there is none which is not a poison. The right dose differentiates a poison]" [18]. This idea forms the basis of much of modern toxicology and pesticide regulation through the use of "thresholds" and dose-response curves, which will be discussed later. Interests favoring weaker pesticide regulation also employ this dictum, arguing that small amounts of chemicals are inherently of low risk given their low dose. For example, the Center for Consumer Freedom, a self-described "nonprofit coalition of restaurants, food companies, and consumers" and opponent of "health care enforcers" and "meddling bureaucrats," used this argument in a 2004 article opposing regulation of acrylamide, a carcinogen found in some foods. "The dose makes the poison," they argue, "practically every substance on earth (including water and Vitamin C) can kill you if it's concentrated enough." They claim that to experience "any real danger from acrylamide," the average person would have to eat over "182 pounds of fries every day, for his or her entire life"

[22]. Many industry organizations, when opposing pesticide regulation, employ similar claims that only outlandish exposures to pesticides can cause harm [7].

Many environmental health scientists contend that toxicology's traditional dictum is no longer appropriate in describing the risks of some heavy metals, like mercury and lead, and many pesticides [23-25]. On the most basic level, scientists and regulators often lack adequate knowledge of "the dose," i.e. the true level of human exposure, and "the poison," i.e. the full toxicity. Better measurement methods and more systematic testing for OPs in food, water, dwellings, and people have shown that older sampling methods often underestimated people's true pesticide exposure, or "dose" [7]. In terms of toxicity, scientists have found that supposed threshold doses, the levels below which no adverse effects are seen, apply differently to developing organisms than to adults. This difference exists largely because of the dependency of a threshold dose on the effect being measured.

The Environmental Protection Agency (EPA) determines an acceptable level of risk by reviewing toxicology studies in which scientists give animals incremental doses of a chemical and then monitor for a proscribed set of effects. The highest dose at which the studies show no effect is termed the no-observed-adverse-effect-level (NOAEL), and is important in setting the human exposure limit for that pesticide. If the studies do not look for a certain effect, however, the NOAEL cannot account for it. Few EPA-reviewed studies examine developing animals or look for subclinical neurological dysfunction, despite ample evidence of harm from outside literature, resulting in a NOAEL and other thresholds that effectively ignore developmental neurotoxicity. The title of this thesis,

"No Observed Adverse Effects," reflects not the absence of harmful effects but rather the unmeasured, at least in a regulatory sense, harmful effects of OPs on developing brains.

Environment in Medicine

Environmental health as a field grew from the work of industrial hygienists, sanitarians, and occupational medicine physicians in the early twentieth century. Prior to this time, physicians and the lay public often regarded the environment and human health as closely interlinked. Vapors and *miasma* in the ambient air, as one example, were considered the cause of malaria (mal'aria or "bad air"), cholera, tuberculosis, and many other diseases before the acceptance of the germ theory [7, 26]. Climate, weather, and geography all influenced physicians' diagnoses, and workers of the era worried about the fumes, dust, and smoke they experienced on the job, despite lacking knowledge or proof of their toxicity [27].

The rise of reductionism in medicine around the turn of the twentieth century slowly separated disease from its surroundings. Illness came to exist only to the extent to which it could be measured, often by limited means, and the causative role of bad air, dust, and odor disappeared with the ascendance of bacteriology. The rise of bacteriology, however, paradoxically reinforced in the public's mind the importance of environmental sanitation, even as microbiological principles shifted physician's concerns from the economic, social, and environmental context to the individual level [26]. The relatively marginalized field of occupational health, called industrial hygiene in the early 1900s, became one of the last remaining bridges of environmental causality [4]. In *Deceit and Denial*, historians David Rosner and Gerald Markowitz detail the works of Alice

Hamilton and Yandell Henderson in the early twentieth century in connecting workers' exposures to lead and other chemicals to their diseases [14]. Yet, industrial hygiene as a profession later embraced the modern ideals of the industrial architecture it served, as the scope of the discipline narrowed and it neglected its earlier ties to environmental medicine. Measurements, laboratory investigations, and narrow statistical analysis were all that could be relied upon, while workers' observations and intuitions about health were generally discounted or overlooked. Occupational medicine, however, remained unique among the medical disciplines in that it never completely abandoned its focus on how the environment, albeit the work environment, affected health [4].

In describing lead's transition from a strictly occupational health issue to a broader environmental health concern, Rosner and Markowitz argue that, until the early 1970s, the roots of the two fields were "essentially distinct: occupational health issues were seen as of interest only to workers and some of their unions, isolated beyond the gates of the factory, in the cauldron of American industrial production" [14]. In contrast, the largely middle class environmental movement was more concerned with protecting wilderness and natural areas from human encroachment and despoilment [28]. As the environmental movement matured, however, these two disciplines, occupational and environmental health, became tightly interlinked.

In the mid-twentieth century, with much of infectious disease "conquered," a shift in medicine from acute to chronic diseases, and the increasingly visible problem of industrial waste, Americans shifted their concerns to the hazards of pollution and synthetic chemicals [16, 26]. Doctors, and more frequently environmental activists, realized that workers were not the only ones susceptible to toxic substances, and that these

chemicals could pass beyond factory walls to pose dangers to the general population [15]. In the 1960s, Citizens organized around local toxic waste threats, and older conservation organizations like the Sierra Club and the Audubon Society often leant their support [16]. Rachel Carson's publication of *Silent Spring* in 1962 brought pesticides, particularly DDT, to the forefront of the environmental movement [29]. The book, largely a synthesis of the burgeoning research on ecology and environmental toxicology, detailed the myriad effects of organochlorine and organophosphate pesticides on humans and wildlife. Concerns about organochlorine pesticides and other chemicals, along with air and water quality led to the creation of the EPA in 1970, a year that also marked the first Earth Day, regarded as a watershed event for the environmental movement [16].

In the 1980s, the momentum of the environmental movement, along with the regulation it generated, inspired the formation of opposition organizations, business roundtables, and politicians decrying the growing bureaucracy and loss of individual rights. These groups found support in President Ronald Reagan's administration, and gained coordination through his successor's Council on Competitiveness. In 1994, their campaign for regulatory relief reached its zenith with the election of a Republican Congress and its Contract with America [7]. It was in this milieu of strong advocates for children's health and the environment on one side and intense industry and political opposition on the other that this Congress passed the landmark FQPA just two years later by unanimous vote.

Mittman *et al*. argue that "environment and health have long been seen as having separate histories" [13]. The EPA, for example, is a major player in nearly all modern environmental histories, yet is virtually absent in the health literature, despite its position

as primary regulator of pesticides and other toxic substances. Perhaps because of its place as a separate agency outside the Department of Health and Human Services, its role in public health is frequently overlooked. At its inception, more than one-tenth of the EPA's employees were commissioned members of the US Public Health Service [30]. Today, the percentage is much lower as more employees now come from the fields of law, policy, and economics.

Medical historian Christopher Sellers, in his paper "The Dearth of the Clinic: Lead, Air, and Agency in Twentieth Century America," writes that "scholars of twentieth-century medicine and public health are only beginning to come to grips with the resurgent biomedical attention to the environment..." [27]. He further urges "medical historians' attention toward environments—workplaces, homes, and the outdoors" and to the "proliferating linkages between chronic degenerative disease, subclinical toxicity, and environmental exposure" [27]. While toxicologists, physicians, and environmental health scientists, as well as lay-activists and industry employees, have directed increasing amounts of attention to the subclinical effects of insecticides and other chemicals, health historians have only recently addressed this development.

Developmental Neurotoxicity

> *The human brain is composed of about 1 trillion nerve cells, called neurons, that are linked to each other in a web of staggering complexity; each neuron in the brain may be connected to as many as 1,000 other neurons…. If the brain is unfathomably complex, only the development of the brain is more so. From a ball of undifferentiated cells, an embryo with specialized tissues develops; trillions of neurons of dozens of specific types are born, migrate to the correct locations, and form the appropriate connections to carry out the*

> *complex functions of the brain.... Killing just a handful of nerve cells early in development can potentially cause profound effects, since those cells might have been destined to produce millions of progeny cells, the absence of which will alter the pattern of connections among other neighboring cells.*
>
> -*Joe Thornton, 2000,* Pandoras Poison's [31]

As mentioned earlier, developmental neurotoxicity has been little studied in the historical literature partially because it is not a disease or an illness. It does, however, have implications for many of the cognitive diseases of childhood, some of which appear to be increasing in prevalence, among them learning disabilities, dyslexia, mental retardation, attention deficit disorder, and autism [32]. Many neurologists and environmental health specialists believe that early life exposure to toxins may have a role as well in the neurodegenerative diseases of old age like Parkinson's and Alzheimer's [33, 34]. As frequently is the case in environmental health, clear causation between exposure and disease is difficult to establish, though evidence of these links is mounting [25]. If indeed developmental neurotoxicants, including lead, mercury, PCBs, and organophosphates, play any significant role in causing these childhood conditions, which affect 5-10% of American children, the potential for harm reduction is enormous [32].

Toxicology, as noted earlier, has historically focused on dose effects. Fetuses, infants, and children are often more susceptible to toxicants than adults partially due to age-related differences in absorption, metabolism, detoxification, and excretion [8]. Traditional dose-response models can account for this type of variation. Yet the remainder of developmental toxicity results from qualitative, rather than quantitative, differences, which according to the 1993 NAS report "are the consequences of exposures during special windows of vulnerability—brief periods early in development when exposure to a toxicant can permanently alter the structure or function of an organ system"

[8]. These effects are irreversible and require an entirely different way of thinking about toxicants.

The notion that doses of chemicals considered safe for adults can cause defects in developing fetuses and children is well established in obstetrics [35]. Physicians minimize the number of medications that pregnant women take and avoid particular ones at all costs for fear of causing birth defects. Yet this relationship was not always understood. Until the 1960s, despite prior evidence to the contrary, medical professors taught that the placenta constituted a perfect barrier "to toxic substances unless given in such high doses as to be lethal to the mother" [35]. British medical historian Ann Dally explores the reasons that this fallacy held sway over the medical profession, despite extensive studies by teratologists. Our present knowledge about the vulnerability of the fetus is in some ways a rediscovery of past beliefs. In ancient Carthage, bridal couples were forbidden alcohol for fear of damaging the child resulting from the wedding night [36]. Through much of the 18th and 19th centuries, doctors gave much attention to maternal impressions, the idea that the emotional state of a mother could harm her unborn child.

The use of thalidomide in Europe in the 1950s to treat morning sickness provides a tragic example of blindness to developmental toxicity and of the failure of communication across scientific disciplines. Both medical professionals and the lay public at that time regarded thalidomide as a safe drug because there appeared to be no lethal dose [36]. However, evidence existed about the teratogenic potential of thalidomide prior to its use and, since the 1930s, teratologists had studied the ability of various chemicals to cause birth defects in mammals. The public, however, was unaware, largely because much of the work had been published in specialty journals and received little

general medical coverage [36]. In 1961, however, four years after the drug first appeared on the market, physicians, beginning with Widukind Lenz in Germany, finally realized the potent teratogenic effects of thalidomide. Nearly 10,000 children in forty countries had been affected [37]. The experience tragically taught researchers that the timing of an exposure could be as important as the dose. For instance, upper limb defects developed when exposures took place during days 27 to 30—exactly at the time when the upper limb buds normally appeared, and lower limb defects occurred with exposure during lower limb bud development [35]. These effects were extremely instructive about the role of chemical signaling in human development and to the sensitive nature of the developing embryo and fetus. Reacting to these events in the early 1960s, the U.S. Food and Drug Administration (FDA) created guidelines that required new drugs to undergo extensive teratology tests on animals [38].

While arm and leg defects are striking consequences of chemical interference, toxicants can cause analogous problems in less visible areas of the body like the brain. One toxicologist posited, decades after the FDA instituted their teratology testing rules, that if "thalidomide had also induced behavioral dysfunction, perhaps detection of functional [neurological] disorders would have been included" in these guidelines years earlier [39]. Yet in the early 1960s, the study of developmental neurotoxicity, or "behavioral teratology" as it was then called, was still very much in its infancy [40]. Though researchers discovered this phenomenon later than most other forms of teratology, the nervous system is actually more sensitive to chemical insult than other organs. Three principal reasons account for this heightened sensitivity. First, the prolonged period of brain development, stretching from the first trimester of pregnancy to

several years after birth, presents a long window of exposure to potential toxins. Second, the central nervous system has little capacity to repair damage, and thus early-life injury is often permanent. Third, and perhaps most importantly, the nervous system is highly specialized and maturation depends on a complex series of nerve cell migrations and transformations, as opposed to organs like the liver and kidney are comprised of many thousands of identical units [41].

In 1961, Jack Werboff, a toxicologist, and Jacques Gottlieb, first documented the phenomenon of developmental neurotoxicity in rats exposed to anticonvulsant medications, but not until the late 1960s and early 1970s, when research on fetal alcohol syndrome showed that behavioral teratology was a widespread cause of mental retardation, did government regulators take notice [39]. In the late 1970s, toxicologists expanded their focus from pharmaceuticals to the neurodevelopmental effects of environmental and industrial toxins, particularly the heavy metals lead and mercury [39]. Studies on these metals provided the background for later work on organophosphates in the 1990s.

The Case of Lead

I have included this brief history of lead to illustrate the evolution in medical thinking as the clinical recognition of lead toxicity has progressed from overt to subclinical to subtle effects [42]. This is relevant because it parallels and anticipates the concerns about organophosphates over a decade later, and because it yields several important comparisons. The discovery of lead's toxicity proceeded along a familiar path among toxins, as effects were first noted in highly exposed workers, then in accidentally

poisoned children, later in patients with persistent deficits following poisoning and recovery, and finally at a subtle, population-level from low-level exposure during development.

Lead is a natural element found abundantly in the Earth's surface, yet it is a substance to which humans and other mammals have had little exposure evolutionarily, and hence developed little capacity for detoxification. Physicians have known of lead's acute neurotoxicity as far back as the ancient Romans, who used the metal extensively in plumbing, pewter, and fortified wine [43]. Around the turn of the twentieth century, paint manufacturers began using lead heavily in the United States and, in 1923, gasoline producers started adding tetraethyl lead to gasoline. Rosner and Markowitz expose the lead industry's willful ignorance and misleading campaigns about lead's toxicity. As early as 1921, the president of National Lead wrote in a letter to the dean of the Harvard Medical School that "fifty to sixty years" of experience had taught the industry that "lead is a poison" [14]. Within the next several years, the same company began an advertising campaign portraying lead as "the doctor's assistant" and promoted the idea that "Lead helps guard your health" [14].

In the early 1900s, lead poisoning was regarded (if it was regarded at all) as an occupational hazard for lead miners and smelters. By the early 1930s, however, pediatricians agreed that lead paint posed a hazard to children [44]. Consistent with the contemporaneous conception of toxicity, it was believed that if a child survived lead poisoning, he or she would recover completely [45]. Scientists have since learned that children develop lead poisoning at lower lead levels than adults largely because their blood-brain barrier is relatively permeable, which allows the metal to concentrate in their

central nervous system [8]. In 1991, the Centers for Disease Control and Prevention issued a statement, entitled *Preventing Lead Poisoning in Young Children.* "Since 1970, our understanding of childhood lead poisoning has changed substantially," the CDC statement asserted. "As investigators have used more sensitive measures and better study designs," it said, "the generally recognized level for lead toxicity has progressively shifted downward. Before the mid-1960s, a level above 60 µg/dL was considered toxic. By 1978, the defined level of toxicity had declined 50% to 30 µg/dL" [45].

That standard has declined to 10 µg/dL today based on further research. What the "better study designs" revealed, was that acute toxicity was only the most obvious of lead's effects. The first inklings of this possibility arose in 1943 when physician Randolph Byers and psychologist Elizabeth Lord at Boston Children's Hospital reported a case series showing that 19 of 20 children who had "recovered" from lead poisoning later failed high school or had behavioral problems [25].

A landmark study in 1979 by Harvard pediatrian and psychiatrist Herbert Needleman marked a major turning point in scientific thinking about lead. The study showed that children with lead levels between 20 to 40 µg/dL—now considered high, but well below the threshold at the time—had lower IQ scores and a higher incidence of "non-adaptive classroom behavior" than children with lower lead levels [46]. This study provided a new way to look at lead's effects, particularly at subtle impairment of neurodevelopment [47]. Policymakers particularly paid attention to the real-world implications of the study, later outlined in the 1991 CDC report, which noted that "a shift in mean IQ score of 4-6 points... was associated with a substantial increase in the prevalence of children with severe deficits (that is, IQ scores less than 80)" and "an

absence of children who achieved superior function (that is, IQ scores greater than 125)" [45].

In the late 1970s and early 1980s, the U.S. government mandated lead's removal from paint and gasoline, based partially on Needleman's findings and other lead data, though largely because lead could harm the new catalytic converters in cars, [43]. The tremendous environmental decline in lead over this period, considered one of the signal victories in the recent history of public health, allowed for a natural experiment [48]. A study published in 2002 found that from 1976 to 1999 the average child's blood lead level dropped by 15.1 µg/dL, which, they calculated, raised IQ scores by about 2.2-4.7 points [47]. This increase in IQ is nearly undetectable in an individual child, but its overall impacts on society are enormous. Statistical and economic studies have determined that an IQ point has a great deal of economic value over a person's life. The authors calculated that the average increase in IQ generated about $56,000 in extra lifetime income for each child, which sums to hundreds of billions of dollars for the childhood population [47].

A study published in the *New England Journal of Medicine* in 2003 concluded that subtle neurological deficits arise at blood levels even below 10 µg/dL, the current standard [49]. Later studies have supported this finding, and further showed that the deficits seen below 10 µg/dL are greater than deficits at higher blood lead concentrations [25]. Based on the accumulated evidence, many lead experts now believe that no threshold effect exists for lead, that is, there is no level that does not produce a toxic effect [50].

Frequently in the history of environmental toxins, stakeholders standing to lose money through government regulation attempt to place blame upon the victim of a

poisoning rather than the toxicant. A corollary of this strategy is to associate the disease with minorities and the poor so as to marginalize the problem and to minimize the risks perceived by the general population. With increasing public awareness of lead poisoning in the 1950s, the Lead Industries Association (LIA) attempted to do just this by shifting the blame from the lead industry to the problem of poverty [44]. A 1952 LIA publication stated, " childhood lead poisoning is essentially a problem of slum dwellings and relatively ignorant parents" [44]. Lack of food, another publication argued, might cause children to eat paint flakes, but even a "well-fed child may still be emotionally hungry because he does not receive as much loving attention as he needs," in effect shifting the blame from a toxin in their products to purportedly negligent parents [44].

In terms of organophosphates as well, physicians often placed blame upon the poisoned farmworker rather than the pesticide or its mode of use. In 1964 the president of the California Medical Association, Ralph Teall, employed racial and economic stereotypes to do just this in a speech to the state legislature about pesticides. "People," he said, referring to farmworkers, "just must be more careful about their personal hygiene if they are going to avoid any difficulty" with pesticides [4]. In general lawmakers have passed little legislation protecting farmworkers unless worried and vocal consumers perceived risks to themselves as well. For example, in the 1960s Cesar Chavez and the United Farm Workers' were most successful when they linked farmworker health and safety to public fear of the persistent organochlorine pesticides [16]. The lack of simultaneous attention to organophosphates, which posed far greater immediate risks to farmworkers, showed the importance of marginalization in avoiding attention and regulation [4]. Even as late as the 1990s, farmworkers, despite their higher exposures,

remained peripheral to the pesticide debate [16]. Though the 1996 FQPA centered on pre- and post-natal exposures, many environmental health experts agree that a focus on children is the easiest way to politically achieve pesticide reductions for farmworkers as well.

Evolution of Pesticides and Pesticide Legislation

While *Silent Spring* brought the public's attention to pesticides on an unprecedented scale in 1962, farmers have used insecticides, and others have fretted about their effects, for over a century. As new pesticides were developed, the pattern and spectrum of use changed, as did human and ecological concerns. I will outline several of the primary classes of insecticide to give a sense of the organophosphates' place in history. Insecticides can be divided into a "first generation," generally those used prior to the 1940s and easily derived from natural sources, and a "second generation," or the synthetic organics, which gained widespread use after World War II and revolutionized the farm industry [51]. Organophosphates are a member of the latter, having been produced in the laboratories of Nazi Germany and applied extensively beginning in the 1950s.

The first generation insecticides included heavy metals, such as lead, copper, arsenic, and mercury, as well as plant-derived compounds including nicotine, rotenone, pyrethrins, and lime [51]. James Whorton notes in *Before Silent Spring* that though the public of the 1970s considered their era the beginning of the pesticide controversy, the widespread use of Paris green (copper acetoarsenite) and lead arsenate incited fierce disputes at the end of the nineteenth century [1]. For example, in 1891 the *New York Times*

created a public panic with a headline entitled “Poison Grapes for Sale,” which were incorrectly believed to contain high residues of arsenic [3]. Yet farmers did use a great deal of both lead and arsenic on crops of the era, and the medical literature contains many reports of farm-worker poisoning from these metals. The government’s management of consumer risks in the 1920s illustrated its affinity and close relationship with industry. As the center of the American apple business shifted from upstate New York to the drier valleys of Washington State, food inspectors found higher levels of lead arsenate dust remaining on fruit. Rather than informing the public, which they feared would create another panic, government regulators instead gently pressured growers over a period of years only to improve application and handling techniques to minimize residual dust [3].

The early twentieth century was a time when little was known about the health risks of pesticides other than acute poisoning, and business interests generally outweighed health concerns. In 1910 Congress, concerned with the lead and arsenate insecticides, passed the Insecticide Act, which was the first American law governing pesticide use. Yet this law was intended to ensure pesticide purity, concentration, and efficacy, rather than to safeguard health [7]. Even as late as 1927, the government had still not evaluated the chronic health consequences of the lead and arsenical pesticides [7]. The earlier Pure Food and Drug Act of 1906 had little initial role in governing insecticides. It did, however, create a division at the Department of Agriculture (USDA) for food testing and enforcement that later assumed responsibility for pesticide control. Health advocates applauded the decision to regulate pesticide residues in food, yet argued that the task should not remain with the USDA, which was primarily a service and booster agency for agriculture, [3]. In 1927, the Department separated its agricultural

research section from its enforcement one, which it renamed the Food, Drug, and Insecticide Division (later shortened in 1930 to the Food and Drug Administration, or FDA) [52]. Not until 1940, two years after the passage of the Federal Food, Drug and Cosmetics Act (FFDCA), did Congress move the regulation of pesticide residues away from the USDA to a health-centered agency [52].

I mention briefly the pyrethroid class of insecticides because its uses have grown substantially in recent years and because it is the only major group to span both the first and second generations. Pyrethrins, the prototypes of the class, derive from the pyrethrum flower, a member of the chrysanthemum family, originally found in Persia and the Caucasus region [1]. People in these areas have used the crushed petals to control body lice since before the nineteenth century, and commercial production of pyrethrins began in the 1840s. In keeping with the major expansion of insecticide production during World War II, Japan became a major producer during the war, which gave it a strategic advantage when fighting in malarial areas. After the war, the pyrethrins, because of their relative weakness and expense, remained a small component of the American insecticide market, despite their relative safety. Over the next several decades, scientists developed synthetic, more stable and effective, versions of these substances, called pyrethroids, which, following the bans on many OCs and OPs, have become among the most widely used indoor and outdoor insecticides in the U.S. They now account for about one quarter of the world insecticide market [53].

The second generation of insecticides, the synthetic wonders of the laboratory, were to pest control of the mid-century what antibiotics were to medicine. Stronger than nicotine or pyrethrins, lacking the obvious health dangers of lead or arsenic, and

possessing an efficacy lasting for months after application, the organochlorine pesticides (OCs), such as DDT, dieldrin, and chlordane, seemed the solution to the pest control problem. DDT's history is, in many ways, emblematic of the problems of nearly all of the organochlorine pesticides. Developed in the 1870s, DDT's insecticidal properties were not discovered until World War II, when military scientists, in a frantic quest to control malaria-transmitting mosquitoes and typhus-carrying lice, tested hundreds of potential compounds for their insect-killing capabilities. DDT proved extremely effective, and American companies manufactured over 2 million pounds per month in 1944, allowing the United States to spray entire Pacific islands before invasion [7].

After the war, despite the consternation of many government scientists, DDT was used extensively in agriculture, forestry, and public health programs. By 1955 more than 90% of all U.S. agricultural pesticides were synthetic organic compounds, and in 1961 DDT was registered for use on 334 crops [8]. DDT's long-lasting insecticidal nature, part of the reason it was so appealing, also accounted for a potential danger: its extreme persistence in the environment. Even when first discovered, scientists knew something of DDT's ability to concentrate in human tissue and breast milk, though little was known about the consequences. Biologists later found that DDT and other organochlorines appeared in exponentially greater doses at sequentially higher stages of the food chain, causing ecological disruption. At the same time, medical researchers increasingly discovered human health risks [3]. Rachel Carson, as discussed earlier, eloquently outlined these concerns first in a series of articles in the *New Yorker*, and later in her book *Silent Spring* [29]. The controversy that ensued eventually caused the United States to ban the use of DDT in 1973, and the remaining organochlorines shortly after.

Bioaccumulation was not the only issue facing the OCs, a more immediate problem was insect resistance. Just as bacteria developed defenses to the widespread use of the antibiotic "wonder drugs" of the 1950s, insects acquired their own mechanisms of evading the organochlorines' attack [7].

During the post-war explosion of new pesticides, many in government realized that stronger regulation was needed to cope with the growing production and use of these new chemicals. In early 1947, the USDA estimated that 25,000 pesticide products had been licensed under the Insecticide Act, and projected that many more would soon arrive. In response to USDA's difficulties in tracking the pesticides already in use, Congress passed the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) that same year, mandating that manufacturers register any "economic poisons" with the USDA [7]. Yet FIFRA lacked a strong enforcement arm, and its primary means of regulation was simply labeling of pesticides. The labels implied to consumers that they could avoid adverse health consequences if they followed instructions on the product. Yet the act contained little provision for examining human or ecological health risks. If a product was found to induce harm to humans even when used properly, the Secretary of Agriculture would declare it "misbranded" [7]. Even then the Secretary was forced to register the pesticide for use, albeit "under protest" [7].

FIFRA remained the primary law governing insecticide use—other than the 1938 FFDCA, which mandated that the FDA regulate pesticide food residues—until 1954, when the Miller Pesticide Amendment to the FFDCA, named after Congressman Arthur Miller of Nebraska, gave the FDA authority to establish maximum "tolerances" of allowable pesticide contamination on raw, unprocessed foods [52]. The Miller

Amendment was the first major pesticide law to integrally consider health, though the law allowed the FDA to consider the economic costs to farmers and consumers when making tolerance decisions [7]. The creation of FIFRA and the Miller Amendment split pesticide regulation into two fragments, putting the USDA in charge of pesticide *registration* and the FDA in charge of pesticide food *tolerances*. The FDA, given the responsibility of protecting health, gained no authority to require tests of pesticide safety from manufacturers and had little data on which to base its decisions. The USDA, on the other hand, required only efficacy data, rather than safety studies [7].

One final piece of legislation from the 1950s deserves mention for its lasting importance in the pesticide debate. In 1958 Congress passed the Food Additives Amendment to the FFDCA following a series of food safety hearings led by Congressman James Delaney of New York. The amendment gave the FDA the power to regulate not only pesticide residues in raw foods, but also residues in the increasingly popular processed foods. The act is more notable because it contained the most controversial provision in pre-FQPA pesticide history, known as the "Delaney Clause" [52]. The initially unassuming clause stated that the FDA should prohibit any pesticide detectable after the processing of food (thereby a food additive) and shown to "induce cancer" [7]. This strict guideline, later feared and reviled by pesticide manufacturers, stood in stark contrast to the risk/benefit situation allowed in raw foods. Another idiosyncrasy of this clause is that it applied only to cancer and not to the many other kinds of adverse effects that pesticides can cause. As I will explain later, abolishing this clause for pesticides was the food industry's dominant reason for supporting the FQPA.

In addition to the above amendments to the FFDCA (the residue side), Congress

passed several amendments to FIFRA (the registration side) that set the stage for the 1996 Food Quality Protection Act. A 1964 amendment finally gave the USDA the authority to terminate, or "cancel," a pesticide's registration. This power became important within the next decade when the newly formed EPA cancelled DDT and many other organochlorines [7]. In 1972 another amendment to FIFRA mandated that the focus of pesticide registration move from efficacy to safety, particularly with regard to health and the environment. The nascent EPA received the enormous new responsibility of assessing health risks for all new and old pesticides with very little data [7]. Over the next two decades, the agency frequently came under fire from all sides for failing to meet congressionally imposed deadlines for pesticide reregistration. This perpetual state of disarray became one of the primary motivators for Congress in passing the strong legislation of the FQPA.

Farmers and insecticide manufacturers lost many organochlorines to bans (and insect resistance) through the 1970s. In their search for substitutes, they increasingly turned to two other groups of insecticides already in use, the carbamates (CMs) and the organophosphates (OPs), which have since become the most widely used insecticides in the world. These pesticides held a distinct advantage over DDT and the other organochlorines. Their relatively short life span allowed them to degraded with exposure to the elements and kept them from concentrating in body tissues. Yet they also had a major drawback: severe nervous system toxicity following exposure. Toxicologists often consider CMs and OPs together because they both act on the insect and mammalian enzyme, acetylcholinesterase (AChE). This enzyme normally terminates the signals between some types of neurons by breaking apart the neurotransmitter acetylcholine.

When carbamates (reversibly) and organophosphates (irreversibly) inactivate AChE, acetylcholine over-stimulates the receiving nerve cell, causing death in insects and nervous system, cardiac, and respiratory dysfunction in humans [20].

Organophosphate Pesticides

> *Symptoms in [mice and rats] started with an increase in respiration, followed soon by unsteadiness, lack of coordination, and scattered muscular twitches. Defecation, urination, lacrimation, and salivation occurred regularly. The severity of symptoms rapidly increased to prostration with generalized muscular fibrillations, body twitchings and tonic and clonic convulsions, followed by death apparently due to respiratory failure of peripheral origin. The heart continued to beat 2 to 3 minutes after cessation of respiration.*
>
> -*K.P. DuBois* et al., *"Studies on the Toxicity and Mechanism of Action of Parathion." 1949*

Not all organophosphates act on cholinesterase or function as pesticides, though all OPs share one thing in common, which is a characteristic phosphate linked to several carbon atoms, hence the term organo-phosphate [20]. Out of the thousands of OPs created after 1945, over forty are insecticidal. While all of these on the same enzyme, they often differ markedly in their potential for acute and chronic neurotoxicity, as well as their level of persistence in the environment.

Organophosphorus compounds were synthesized by Lassaigne in the early 1800s by mixing alcohol with phosphoric acid [54], but Phillipe de Clermont, in 1854, first described the synthesis of an organophosphate in a report to the French Academy of Sciences [20]. Not until 1932, were their potential effect on the nervous system discovered, when Willy Lange and Gerde von Kruger noticed visual changes while testing dimethyl

and diethyl phosphorofluoridate [54]. Later in the 1930s, Gerhard Schrader, a chemist at the German firm I.G. Farben and the father of modern organophosphates, began exploring their insecticidal potential. In 1937, Schrader, at the request of the Nazi government and I.G. Farben, traveled to Berlin to demonstrate these compounds' potential as chemical warfare agents. The Germans soon found certain OPs to be extremely potent nerve agents and created the G series compounds (tabun, sarin, and soman), which were not deployed in World War II [6].

British chemists at Cambridge University, Hamilton McCombie and Bernard Saunders, in 1941 independently synthesized a neurotoxic, though less potent, organophosphate of their own, called diisopropyl fluorophosphate (DFP). As part of the war effort, Cambridge chemists routinely tested compounds on themselves. Among them was Fred Pattison who, in a later interview, noted that he became "virtually blind for about 10 days" following an intentional exposure to DFP [55]. In the 1950s, the United Kingdom created another nerve agent, called VX, which had many times the potency of the G series, and has never been used militarily. Belying the image of organophosphates as short acting and rapidly dissipating, the military referred to VX as a "terrain-denying" compound because it persisted in target areas for days to weeks after application [20]. The nerve gas roots of the organophosphate pesticides have carried potent symbolic meaning throughout the rest of their history. After an accidental release of VX gas killed thousands of nearby sheep in 1968, historian Linda Nash notes that "farmworker advocates began referring to agricultural spraying as 'chemical warfare' and to parathion as a 'nerve gas'" [4].

Despite knowledge of DFP, Americans knew little of OPs as insecticides until the

end of World War II, when government investigators discovered Schrader's laboratory. Schrader himself then wrote an unclassified American report outlining OPs' insecticidal activity, including details about some of the more than 2000 OPs his laboratory had synthesized. American companies capitalized on this discovery and, free of patent or licensing restrictions, began manufacturing large quantities of organophosphate insecticides, beginning with Monsanto's TEPP in 1946 [6]. Dozens of OP insecticides followed, including parathion in 1949, and malathion and azinphos-methyl in the 1950s [4]. Though more dangerous to use than the aforementioned organochlorines, OPs gained popularity through the 1950s due to their low cost and broader insecticidal spectrum. Researchers found that parathion could kill all insect species against which it was tested. Farmers employed this property, using organophosphates to control "secondary" pests that were inherently resistant to DDT. Farmers found another benefit in that plant roots absorbed the OPs and distributed the chemicals to the stems and leaves, which allowed for more systemic poisoning of insects [6].

During this time of rapid expansion, scientists were also at work determining the OPs' mechanism and toxicity. George Koelle and Alfred Gilman (later co-author of a prominent pharmacology textbook and father of Nobel-prize winner Alfred Gilman Jr.), pharmacologists in the Army Chemical Corps at Edgewood, Maryland, first identified organophosphates' neurotoxic mechanism through its inhibitory effects on acetylcholinesterase [56]. The link between OP nerve gases and insecticides remained a prominent factor in research. In 1953, the military Chemical Corps funded research at Johns Hopkins School of Medicine that tested nerve gases and parathion on human subjects, who often took days to recover [6]. For the next several decades, physicians

focused primarily on the acute effects of OP poisoning, largely unaware of any chronic and developmental consequences. This despite University of Chicago toxicologist Kenneth Dubois's conclusions in 1949 that "continued exposure to sublethal doses of parathion results in subacute poisoning in rats and suggests the possibility of a cumulative action by parathion in other animals" [57].

Doctors focused on acute OP poisoning for good reason, given its widespread prevalence and lethality, and because it was relatively difficult to diagnose. Though the poisoning resulted in a characteristic physiological response, including sweating, salivation, tearing, vomiting, defecation, and difficulty breathing, less severe cases could be confused with other, more common, illnesses [20]. Physicians treated thousands of people, many of them farmworkers, for organophosphate poisoning in the 1950s and 1960s, though likely many more went undiagnosed. Berton Roueché, the famed medical writer for the *New Yorker*, wrote two "medical mysteries"—"The Dead Mosquitoes" and "The Fumigation Chamber"—with the surprise diagnosis of organophosphate poisoning, a testament to the pervasiveness, yet relative obscurity, of the affliction [58].

One chronic complication from a number of organophosphates was particularly evident. Few physicians could fail to realize the debilitating effects of organophophate-induced delayed polyneuropathy (OPIDP). Contrary to acute OP poisoning, its symptoms began several days to weeks after exposure and were caused by a breakdown in certain neurons and their myelin sheaths [59]. Scientists described the syndrome even before organophosphates began their work as insecticides, from an organophosphate solvent called tri-ortho-cresyl phosphate (TOCP). In 1899, the first OPIDP outbreak of paralysis occurred in France after patients drank a TOCP-contaminated creosote oil

treatment for tuberculosis [60]. The syndrome gained notoriety in the United States during the late 1920s and early 1930s, when twenty to sixty thousand men in the South and Midwest developed pain and weakness in their arms and legs after drinking a medicinal beverage called "Ginger Jake." The drink, sold in drugstores, normally contained a Jamaican ginger extract with a high concentration of alcohol. Poor white southerners frequently used Ginger Jake to circumvent prohibition laws [61]. One particular manufacturer found TOCP a cheaper additive than ginger extract, and men who received this adulterated form developed permanent neurological damage. The scale of the tragedy was reflected in the blues music of the period, which frequently sang of the "Jake Leg" or "Jake Walk," referring to the limping gait of the victims [61].

Investigators later found that organophosphate pesticides, including dichlorvos and mipafox, could also produce OPIDP [54]. TOCP, unlike the OP pesticides, had no anti-cholinesterase activity, meaning that the syndrome was unrelated to the pesticides' primary effects on cholinesterase. Toxicologists first suspected the involvement of a separate enzyme, which they called neurotoxic esterase, though they now consider the syndrome related to an OP-induced breakdown in the cell's support structure [20]. The case of OPIDP demonstrated that OPs have effects on the nervous system distinct from those on cholinesterase, the primary marker in OP regulation. This independent mechanism foreshadowed the non-cholinergic consequences of developmental neurotoxicity over a half-century later.

Aside from the distinct syndrome of OPIDP and a related "intermediate syndrome," the medical profession generally overlooked OPs' potential for chronic neurotoxicity through the 1950s and early 1960s, despite increasing use and thousands of

poisonings. Yet researchers recorded chronic effects in specialty journals, and reached a relatively small audience during this period. A progression similar to lead is evident in the medical literature as acute effects were predominantly studied first, followed by chronic effects, then effects on children, and more recently effects on the developing nervous system. In 1961, Australian pharmacologists, in a case study of 16 patients who had recovered from acute OP poisoning, noted residual neurological effects including "severe impairment of memory and difficulty concentrating" [62]. In 1962, Rachel Carson noted these first inklings of residual effects in *Silent Spring* [29]. Through the rest of the 1960s, investigators increasingly looked for, and found, evidence of chronic sequelae from OP poisoning, particularly from occupational exposures [63, 64]. Toxicologists, too, were busy during this period. Starting in 1963, scientists found evidence of more intense poisoning from malathion in young rats compared to adults [65].

Findings of developmental neurotoxicity in OPs lagged somewhat behind those seen in lead. A study done in 1977 showed neuromuscular impairment in adult rats after intra-uterine exposure to low doses of diazinon [66]. The next set of experiments, performed in the mid-1980s, revealed that fetal rats exposed to methyl parathion and parathion had "altered postnatal development of cholinergic neurons and... subtle alterations in selected behaviors of the offspring"[67, 68]. By the late 1980s, however, developmental neurotoxicity research on organophosphates remained in its infancy. Meanwhile, independent and EPA scientists had acquired extensive experience with neurodevelopmental effects from other substances, including lead, mercury, polychlorinated biphenyls (PCBs), anti-seizure medications, and alcohol [69].

In 1989 the state of knowledge had progressed far enough that the EPA held an

agency-wide workshop to create a standardized system testing to test for developmental toxicity. Results from this workshop appeared in the journal *Neurotoxicology and Teratology* in 1990. Although the article praised the agency for its forward thinking, it declared that American "regulatory agencies have been slow to take action," noting that Great Britain and Japan began testing compounds for this problem in 1975 [21]. Prior to the workshop the EPA had no developmental neurotoxicity tests for OPs; rather, they required only one chronic neurotoxicity test—for delayed neurotoxicity (the type seen in the TOCP "ginger jake" paralysis) in adult hens—for this pesticide class [21]. In 1991, based on this workshop and the advice of its Science Advisory Panel (SAP), the EPA issued "generic" developmental neurotoxicity testing guidelines, though not specifically for organophosphates or other pesticides [21]. Increased interest on the subject spurred university-based scientists to conduct further research, and by the time of the 1993 NAS report, researchers had published several studies on developmental neurotoxicity from organophosphates [70]. Yet despite these advancements, the EPA was slow to call for developmental neurotoxicity studies. As late as 1998, the agency had reviewed only twelve DNT studies on insecticides.

Aside from brewing concerns about developmental neurotoxicity, the early 1990s contained a shifting undercurrent in the momentum of pesticide regulation as a whole. As we will see, expanding scientific study and better data, on both pesticide exposure and adverse health effects, began to change the dominant paradigm from economics to health. The most public form of this shift, the publication of the 1993 NAS report *Pesticides in the Diet of Infants and Children*, brought wider attention to these chemicals and set the stage for the 1996 Food Quality Protection Act. In the following pages, I chronicle the

promise and reality of this landmark piece of legislation and trace the growing influence of developmental neurotoxicity in the pesticide risk calculus.

The 1996 Food Quality Protection Act

> *This Act comes to our desk — to my desk and to our administration – with the support of farmers and environmentalists, consumer groups and agribusiness and the medical community. After more than a decade of work, these groups have come together to say with this bill, we do not have to choose between a clean environment and a safe food supply and a strong economy.*
>
> *-President Bill Clinton, August 3rd 1996, Bill Signing of HR. 1627 (FQPA)* [71]

As I stated earlier, the two key events in the recent history of organophosphate pesticides include the 1993 NAS report and the 1996 Food Quality Protection Act. In the late 1980s and early 1990s, many health officials, including toxicologists at the EPA, developed renewed interest in the toxicity of older pesticides following the realization that nearly all of the exposure data and animal studies had been conducted on adults, and that little attention had been given to the increased susceptibility, now well-documented, of infants, children, and fetuses [21, 72]. Based on these concerns, Congress requested that the National Academy of Sciences appoint a committee in 1988, as part of its National Research Council (NRC), to study "scientific and policy issues concerning pesticides in the diets of infants and children" [8]. Congress specifically charged the committee with determining the state of knowledge about exposures, the adequacy of the current laws, and, most relevant to this analysis, the "toxicological issues of greatest concern and in greatest need of further research" [8].

In its report, published five years later, the committee found a number of deficiencies in the current regulatory system. Fundamentally, the report noted that the

EPA lacked good exposure data and thus had poor estimates of children's vulnerability to various pesticides. From the existent data, however, they did find that children were exposed to quantitatively higher levels of pesticides than adults because they consumed more food and water relative to their body size, ate more of some types of pesticide-prone food—like apple juice and applesauce—and possessed immature detoxification systems [8]. These findings, while new to pesticide regulation, fit the traditional toxicological modeling of chemical exposure, inputs, and outputs. Still the committee also noted what they termed "qualitative differences" in the effects of pesticides on children and adults, resulting from the state of growth and differentiation in the former. In terms of developmental neurotoxicity these qualitative differences are most relevant, and indeed the report noted that studies "strongly suggest" that "exposure to neurotoxic compounds at levels believed to be safe for adults could result in permanent loss of brain function if it occurred during the prenatal and early childhood period of brain development" [8]. The committee also stressed that, for pesticides, "neurodevelopmental effects must be part of the battery of end points evaluated," and that "greater attention is needed to develop a broader understanding of the principles guiding developmental toxicity" of humans [8]. As we will see, the first prescription has been only partially fulfilled by the EPA, while university scientists have tremendously broadened the understanding of developmental neurotoxicity.

The report's publication in 1993 found a receptive audience in the newly inaugurated Clinton Administration, which became a strong supporter of pesticide reform [73]. The report also renewed the attention of environmental groups, which had shied away from the pesticide issue since a Natural Resources Defense Council-inspired 1989

"CBS 60 Minutes" report on carcinogenic effects of the pesticide Alar caused major public relations problems [74]. Despite the scientific support from the NAS committee and powerful political proponents in the mid 1990s, the prospect that a Food Quality Protection Act incorporating nearly all of the report's recommendations might pass seemed unlikely, especially given the staunch opposition from agricultural advocates, chemical and pesticide manufacturers, and the Republican-controlled Congress [73]. Yet in August of 1996, in a move that surprised many environmental and health advocates—then-EPA assistant administrator Lynn Goldman remarked, "A million people told us we would never get something like this through"—Congress passed the Food Quality Protection Act by a unanimous vote [2, 10].

The Food Quality Protection Act, actually an amendment to both FIFRA and FFDCA but a substantial piece of legislation in its own right, represented a monumental shift in the regulation of pesticides, and stands as a rare example of the precautionary principle enacted into American law. Though several versions of the bill circulated through congressional committees for years, the final votes took place with very little floor debate (just 28 seconds in the Senate), which is perhaps one of the factors that allowed the law to pass [75]. On the surface the bill contained several provisions calculated to win support from both health advocates and pesticide manufacturers. From a health perspective, the law eliminated requirements that EPA consider the risks and benefits of a pesticide when making regulatory decisions; rather, the law simply directed that the EPA consider health risk. In a major victory for children's health advocates, the FQPA also instituted an extra ten-fold safety factor (referred to as the 10-X provision) instructing the EPA to reduce allowable pesticide tolerances by a full order of magnitude

unless “reliable data” could show that a weaker standard would not cause “pre- and post-natal toxicity” [2]. This new provision, based on advice from the NAS report, was a reversal of traditional risk assessment, for it mandated reduced exposures based on reasonable suspicion and without concrete evidence of harm. The EPA, on rare occasion, had used a similar extra safety factor prior to the FQPA, but only in the setting of strong evidence for adverse effects or glaring omissions in a pesticide’s toxicology database. The FQPA extended this safety factor to all pesticides and then stipulated that it be removed only with strong evidence of safety.

As even the most casual observer is sure to note, the terminology and regulations surrounding pesticides can often be esoteric, complex and counterintuitive. To cancel a pesticide use is to ban it; for example, the EPA cancelled all of DDT’s uses in 1973. A tolerance is the maximum limit for pesticide residue in food, e.g. EPA’s highest tolerable amount of malathion remaining on apples is the tolerance for malathion on apples when they leave the farm. The highest dose of a pesticide that does not harm rats or other experimental animals is called the “No Observed Adverse Effects Level,” or NOAEL. This level is set by exposing thousands of animals to varying levels of pesticides and monitoring the effects. The ten-fold, or 10-X, “safety factor” (sometimes referred to as “database uncertainty factor”) set forth in the Food Quality Protection Act is slightly more complex, and is an extension of two uncertainty factors used in traditional risk assessment. Prior to the FQPA, EPA regulators determined the allowable level of exposure for a given pesticide, like malathion, by determining the NOAEL in animals, then dividing that amount by a factor of ten, and then ten again, to estimate “safe” dose for the pesticide. The first division by ten is supposed to account for possible biological

variation in the response to malathion between humans and experimental animals, while the second ten-fold reduction accounts for differences between individuals within a species. The FQPA's 10-X provision comprised a *third* ten-fold reduction in allowable exposure from the NOAEL, this time to prevent risks to developing infants and children. The main point of this reduction, proponents argued, was that the EPA had calculated the NOAEL based on adult studies that told little about effects on developing organisms. As we will see, the complexity of this concept was an important part of the bill's passage.

The FQPA also introduced two new terms for risk assessors, "aggregate risk" and "cumulative risk," which represent major changes in pesticide regulation. Prior to this bill, the EPA set tolerances for pesticides individually and considered only the exposures from food, ignoring that nearly every individual was exposed to many pesticides daily and through various means. The new "aggregate risk" section required that the EPA consider all pathways of exposure, not just food, but also drinking water, residential, and occupational exposures together. The "cumulative risk" section stated that the EPA must take into account the additive effects of exposures to all pesticides with a common mechanism when setting tolerances, the organophosphates' effect on cholinesterase being the prime example [2]. For a child exposed to thirteen different types of OPs (about average for an American), the old methodology would examine each pesticide's level as if none of the others were present [76]. The new standard would take into account all nine insecticides and look for additive or synergistic effects from this mixture.

Despite these concessions to the health side, industry groups gained one significant victory, the elimination of the feared Delaney Clause as it was applied to pesticides. In 1992, just four years earlier, the Natural Resources Defense Council

(NRDC) won a lawsuit allowing for easier application of the clause (which applied a "zero risk" standard to any carcinogenic food additive), and many in the food industry were concerned about losing products to cancellation under this rule. In 1998, two years after the bill passed, an article in *Chemical Market Reporter*, an industry trade journal, continued to focus on the clause, claiming that "the FQPA was designed to replace the outdated, zero-tolerance Delaney Clause with realistic, safe and science-based pesticide residue tolerances" [77]. According to Ken Cook, a person heavily involved in the FQPA negotiations as co-founder and president of the Environmental Working Group, the structure of the debate in the House Energy and Commerce Committee had much to do with the bill's success [73].

Before describing the activities of the abovementioned committee, I must make another note on terminology relevant to its proceedings. Though I often categorize the "industry" position as monolithic in this paper, it is important to make a distinction between the food processing industry and the pesticide industry. The food processing industry primarily wanted to eliminate the Delaney Clause, whereas the pesticide producers and consumers held a much greater stake in the overall regulatory outcome. Perhaps equally important to note is the fact that the committee chose their "industry" representative from the food processors, who possessed more political clout than the pesticide manufacturers.

In early 1996 committee chairman Tom Bliley (R-VA) organized a small drafting team in the hopes of negotiating a compromise bill. The team included Henry Waxman (D-CA), ranking Democrat in the Health Subcommittee; John Dingell (D-MI), ranking minority member of the Commerce Committee; two lobbyists, one of whom was from the

Environmental Working Group and other of whom was from “industry;” and representatives of the EPA and FDA [75]. Notably absent from this group were representatives from the pesticide manufacturers. While Waxman and the environmental lobbyist actively pushed for pesticide reform, the lone food processor “industry” member was concerned with eliminating the Delaney Clause. The committee produced a bill containing nearly all of the 1993 NAS report’s recommendations, and which was nearly identical to the FQPA later passed by Congress. Several observers note how the pesticide industry, agriculture groups, and most members of Congress knew little about the potential ramifications of many of the bill’s provisions; instead, and perhaps because of the complex nature of the provisions, many supported a bill that they might have otherwise opposed [73, 75, 77]. Congressman Charles Stenholm (D-TX), ranking Democrat on the House Agriculture Committee later remarked, “Most people didn’t know what was in it, not even me” [10]. Some observers later noted, however, that lawmakers’ claims of ignorance might have been a somewhat disingenuous attempt at disassociation from suddenly unpopular legislation. Perhaps the act garnered many votes, in addition to either genuine support or a lack of understanding, because many conservative members of Congress found it difficult to vote against a bill advertised as protecting children’s health. These conservative representatives likely faced political pressure to support an environmental act. In fact, a newspaper article noted the Republican Party’s poor approval ratings in mid-1996, particularly on environmental issues, following a government shut down earlier that year, and speculated, “GOP leaders desperately wanted a quick environmental victory, especially with the Republican National Convention—and the nomination of Dole as the party’s presidential candidate—

approaching in a matter of weeks" [10].

On August 3rd, 1996, President Bill Clinton signed the law almost immediately after Congress passed it. In his remarks at the signing ceremony, he stated that the act "puts the safety of our children first" by setting a "high standard—if a pesticide poses a danger to our children, it won't be in our food, period" [71]. The FQPA now posed an enormous challenge for the EPA, an agency already falling behind on pesticide tolerance reassessments for over two decades [7]. The act required the agency to review nearly 9,700 pesticide tolerances (each pesticide has many different tolerances, e.g. parathion with apples, parathion with strawberries, parathion with corn, etc.) within ten years. The first third was to be finalized by August 1999, the second third by August 2002, and the final third by August 2006. Furthermore, re-registration decisions had to use the new health-based standards, including the ambitious cumulative and aggregate risk mandates and the unprecedented 10-X provision [2]. Much of this was imposed upon a rather reluctant staff at the EPA, many of whom were unaware of the new law until it passed. Daniel Barolo, the head of the EPA's pesticide office at the time, underscored the suddenness of the FQPA, saying "To say we were surprised to learn about this is putting it mildly" [10].

Total Organophosphate Elimination?

> *If you don't like bugs, 1998 could be a bad year. For in the next six weeks, the Environmental Protection Agency may promulgate the most sweeping anti-insecticide regulations in U.S. history. If it does, billions of dollars worth of crops may be lost annually, children may die from cockroach-related asthma and fire ant bites, and Lyme disease-carrying ticks may proliferate. And you may find that some of those raisins in your raisin bran,*

well, aren't.

-Michael Fumento, April 2, 1998, Editorial in the Wall Street Journal [78]

"In my mind, FQPA stands for 'farmers quit planting in America'."

-A farmer from Michigan, quoted on the ACPA Website, July 1998 [79]

"FQPA could become Idaho agriculture's Waterloo, its Gettysburg, it's that serious...OPs are our antibiotics, carbamates our sulfa drugs."

-Pat Takasugi, Idaho Dept. of Agriculture, at EPA hearing in Boise, July 1998 [79]

In March of 1997, when the EPA announced how the FQPA implementation would proceed, farming groups and pesticide manufacturers began to realize the possible implications of the law and became worried about possible cancellations or bans. The EPA declared its review would begin with the 39 organophosphates, due to their high potential for toxicity (one group termed it "Worst First") [79]. In response, several groups, most prominently the American Crop Protection Association (ACPA)—an organization representing the pesticide companies—and its president Jay Vroom, began a public relations campaign to discredit the law and weaken implementation [80]. They made frequent calls for "sound science" in risk assessment, and claimed that the EPA implementation of the precautionary 10-X provision was "driven more by unnecessarily strict interpretation of the legal language than by thorough scientific evaluation" [77, 81]. Daniel Byrd, a toxicologist writing for the libertarian Cato Institute in 1997, generally summarized these arguments by claiming that "science got walloped in the FQPA," particularly in regard to the 10-X provision [75]. "The ultimate casualty," he continued, "likely will be the health of Americans, especially the poor," because "decreased pesticide use" will lead to "more expensive food, diminished food availability and poorer

food quality" [75]. In an attempt to protect Americans from "the negligible health risks from pesticides on foods," he concluded, the Food Quality Protection Act "may well protect some of us from quality food" [75]. Byrd's argument that the FQPA would actually harm human health rather than enhance it would later become a popular criticism of the law.

In addition to the external political and public relations disputes over the FQPA, disagreement within the EPA existed as well. Clinton Administration political appointees struggled to convince EPA career toxicologists and regulators that the new law, and particularly the 10-X safety factor, required fundamental changes from the agency's long-standing practices [82]. Many environmental and health advocates, including agency chief Carol Browner and assistant administrator Lynn Goldman as well as EWG and NRDC, wanted a strict interpretation of the clause, true to its precautionary intent, and an immediate imposition of the safety factor on all pesticides for which the EPA lacked developmental studies. Pro-pesticide groups and many agency toxicologists claimed that the extra safety factor should only apply if the agency possessed evidence of harm [82]. An obvious tension regarding the 10-X factor existed between the "precautionary principle," acting to prevent potential danger without waiting for full evidence, and "sound science," acting only if clear evidence exists. A late-1997 pesticide review sparked by Congressman Henry Waxman admitted that the EPA had applied the 10-fold safety factor in only nine out of 90 tolerance decisions to date, though the agency lacked developmental data for nearly all pesticides [82]. Although this substantial tightening of some tolerances would have been a victory for environmental groups under pre-FQPA legislation, the NRDC saw the partial application as an abandonment of the FQPA's

precautionary intent. Al Meyerhoff, a lawyer from the NRDC, said, in response to the report, “We are witnessing the slow dismantling of the new statute, and it is a sad sight” [82].

By February of 1998, as the EPA steadily labored in the background, the public outcry reached a fevered pitch, particularly around organophosphates. On the fifth of that month, a leaked agency document, which outlined several different scenarios for organophosphate management—including total cancellation, possibly even by May—created an upheaval in the farm and industry sectors [80]. Though the briefing paper was written deep within the bureaucracy and only for discussion purposes, many took it to mean that a blanket prohibition was very likely, if not inevitable [10]. Reassurance from EPA officials that a ban was extremely unlikely and that no pesticides would be cancelled that year did little to improve the situation. A February 25th memorandum written by chief EPA administrator Carol Browner to other senior agency officials further complicated matters by bringing attention to the precautionary 10-X provision. The memo generally echoed the text of the FQPA, stating that in situations where the EPA was uncertain about the need for studies on child-specific concerns, “then that uncertainty itself should mandate application of an additional safety factor" [83]. ACPA president Jay Vroom charged that the memo “profoundly illustrates political mischief is underway,” and claimed that the EPA was advancing the environmentalists’ agenda by “unconditionally and incontestably” implementing the 10-X safety factor [83]. He contended that environmental groups “want scalps on the wall” and a ban on many pesticides by refusing to wait for “sound science” [83].

Based on the leaked memo about total OP cancellation, the pesticide industry

launched a massive lobbying campaign [10]. A 1998 report by the Consumer's Union (CU)—a self-described nonprofit consumer organization and publisher of *Consumer Reports*—accused Vroom and the ACPA of creating the public panic by organizing a "campaign of fear" with a "rumor that EPA is planning an immediate ban of an entire class of insecticides, the organophosphates" [79]. The CU report supported its claim with contemporaneous statements from the 1998 ACPA website (no longer available) about the possible ban: "If, as has been rumored, EPA cancelled all OP registrations at once... an outbreak of the Mediterranean fruit fly in California or Florida could quickly devastate as much as 50 percent or more of each state's fresh produce business," and "in apple-growing regions, growers would find their crops so infested by insect larvae that the fresh-apple market would be virtually destroyed" [79]. It also quoted an advertisement in several farming magazines sponsored by the ACPA and Farm Bureau, which depicted a flyswatter with the caption, "Act now! Or this may be the only pest control tool you'll ever use again!" [79]. The ACPA sent over 20,000 brochures and faxes to growers across the country urging them to apply "political pressure" [10]. These tactics were evidently successful in precipitating alarm among the agricultural community. A May 1998 article in *Wallaces Farmer* confirmed that, "farmers fear the loss of insecticides in the organophosphate family" [84].

Facing pressure from farmers concerned about the potential loss of the OPs as well as the use of the 10-X child safety factor, Congressmen from agricultural states undertook several steps to slow the FQPA implementation. As the *Washington Post* later noted on the subject, the law seemed destined to become "a classic example of how the complex process of agency rulemaking is often far more important that congressional

legislating" [85]. In early April 1998, two Southern Democrats, Charles W. Stenholm of Texas, a cotton grower himself, and Marion Berry of Arkansas, appealed to Vice President Al Gore to step in and calm the situation. In Stenholm's words, some in the EPA "appeared to be running amok" [10, 86]. Thus, on April 8th, 1998, Gore, despite his strong environmental ties, sent a four-page memo to the EPA instructing the agency to work more closely with the USDA, whose views more closely resembled those of the farm and pesticide industries, and requesting that the EPA increase consultation with these industries in the review process [86]. Though many health and environmental groups saw this move as an act to stall the pesticide review, Ken Cook of EWG commented, "I have a hard time concluding that it is… any kind of sellout…. It is a bone that is being thrown out to the agriculture interests, it seems to me, that really anticipates tough decisions" [81].

In response to the Vice President's memo, the EPA created the Tolerance Reassessment Advisory Committee (TRAC), which allowed for greater stakeholder input, particularly from the pesticide industry and farm groups. The committee was far from balanced, and food, agriculture, and pesticide industry groups outnumbered environmental and consumer groups twenty-four to seven [10]. Within a year, all seven TRAC members representing environmental and health organizations resigned. They expressed their opposition to the committee in a letter to the EPA, stating that their "worst fears have been realized" and that, through "endless debate," the process created "a tremendous drain on agency resources and has delayed concrete EPA action to protect America's children" [77]. Consumer's Union later described the committee as a forum to "re-open the debate about whether the 10-X provision was justified (a debate Congress

had already resolved with its unanimous vote)" [87].

Consumer groups, pesticide lobbyists, and agriculture advocates attacked the EPA from all sides. On June 25th, 1998, the House Agriculture Committee held hearings in which the EPA was castigated for its actions on the FQPA [88]. Several congressmen decried the lack of transparency in EPA's actions, and chairman Bob Evans of Oregon claimed that the agency was "rejecting the opportunity to ask for the scientific data" [88]. Perhaps most telling about the FQPA and the public outcry that surrounded the OPs was a statement by Arizona Farm Bureau President Bob Evans. He claimed, "The agricultural community and members of Congress were repeatedly reassured by EPA that FQPA was merely the codification or formalization of existing EPA authority," adding, "This is the source of our greatest sense of betrayal" [88].

To support their efforts in Congress, the Farm Bureau commissioned agricultural researchers at Texas A&M and Auburn universities to conduct economic and crop analyses to show the potential losses from the speculated total ban on organophosphates and carbamates [89]. The reports concluded that the ban would cause "more food imports from foreign nations, higher food prices for American consumers, less consumption of nutritionally important fruits and vegetables, lower crop yields and increased production costs for America's farmers;" in all, the United States would lose $17 billion [90]. The Farm Bureau also funded a study by the Harvard Center for Risk Analysis examining the potential adverse health consequences from this type of ban, which concluded that a ban could result in the premature deaths of up to 1,000 Americans per year [91, 92]. Based on these results, Farm Bureau president Dean Kleckner concluded, "The incomplete science EPA is proposing to implement this law with will result in all pain and no gain," and that,

"the only winners are foreign farmers over whom EPA has no control" [93].

In 1998, Consumer's Union and the Environmental Working Group conducted analyses of their own on the health risks of organophosphates to children. Reports from both groups used government data to conclude that the elimination of certain "risk drivers," or certain pesticide-food combinations, would drastically reduce OPs' risks to children – a far cry from calling for a total organophosphate ban. EWG's report, entitled "Overexposed, " claimed that about one million American children consume "an unsafe dose of organophosphate insecticides" daily, and that 100,000,000 children were exposed to a food dose ten times the acceptable limit, based on government data [94]. The EWG called for several targeted (and prescient) actions to reduce this daily exposure, including the elimination of indoor OP uses, the removal of OPs from crops used in baby food, the cancellation of five high risk OPs (including chlorpyrifos, methyl parathion, and azinphos methyl), and the requirement for developmental neurotoxicity studies [94]. CU's "Worst First" report prescribed similar actions, identifying forty insecticide uses on nine types of fruits and vegetables (a very small segment of total OP use) consumed frequently by children, namely apples, pears, peaches, grapes, oranges, green beans, peas, potatoes, and tomatoes [79]. CU also emphasized that, contrary to industry claims, there were "many viable alternatives to high-risk OP" insecticides, evidenced by the fact that "most growers of the nine crops… *already* get by without using these high-risk chemicals" [79]. Both the CU and EWG contended that the pesticide industry had exaggerated the possibility of total OP cancellation.

The EPA worked slowly to meet the August 1999 deadline for the first third review of pesticide tolerances. As part of overall pesticide reassessment, the EPA was

now forced to consider the adverse health effects of pesticides on the developing bodies and brains of infants and children. Since the early 1990s, research on the subject had grown substantially, leading the EPA to consider developmental neurotoxicity as the "critical effect" in setting protective standards for OPs [87]. University toxicologists had studied developmental neurotoxicity in many OPs, the most impressive findings of which came from a series of studies at Duke University on a widely used organophosphate called chlorpyrifos. In 1997 Duke scientists published a study demonstrating significant distortion of rodent brain development with "cellular, synaptic, and behavioral aberrations" after exposure to chlorpyrifos doses far lower than those necessary to cause acute toxicity or even changes in brain weight (one of the few endpoints examined by EPA studies) [95, 96]. This growing body of academic research on neurological consequences of low-level OP exposure, coupled with the EPA's resolution to focus OP regulation based on developmental neurotoxicity, helped the agency more thoroughly assess pesticide tolerances appropriate for infants and children.

In 1998 the EPA's Scientific Advisory Panel, determining that the agency lacked necessary data on developmental neurotoxicity, strongly recommended that tests of "cognition, memory, and other higher brain functions be included in the neurotoxicity assessment" [97]. The panel also reinforced the precautionary intent of the FQPA, perhaps in response to the tumultuous and antagonistic political climate, stating, "if appropriate toxicity data are not available, the FQPA 10x safety factor should not be removed" [97]. The next year, based on these recommendations, the EPA began requiring developmental neurotoxicity studies from all manufacturers of OPs [98]. Many children's health advocates saw this requirement as a major step towards safer pesticide use and

fundamental to the FQPA's implementation. As we shall see, however, the results of this early promise remain largely unfulfilled today. EPA collected only a handful of DNT studies by the end of the 10-year FQPA process, and has not completed any systematic review. Moreover, the agency, with a few significant exceptions, used no developmental neurotoxicity data in setting pesticide tolerances despite vocal complaints from its Scientific Advisory Panel, a scathing report from its Inspector General, and protests from health groups and scientists.

Enforcement Begins

> *That chemical manufacturers contend there is no evidence to prove these chemicals may cause subtle but adverse effects on behavior and cognitive abilities isn't surprising. You can't find what you don't look for. The fact is, pesticides known to be toxic to the brain have not been tested for these impacts on the young and cannot be assumed safe for developing children under the current EPA limits.*
>
> *-Jeannine Kenney, April 22, 1998, Letter in the Wall Street Journal* [99]

By the summer of 1999, with the August deadline for the first third of pesticide reviews rapidly approaching, the EPA faced a difficult set of options. The agency was expected to make re-registration or cancellation decisions on the 39 priority organophosphates, and nearly every option seemed sure to result in a lawsuit from one side or the other. So, the agency negotiated a compromise solution with the four primary manufacturers of two of the most dangerous OPs. In conjunction with the pesticide manufacturers, who remained angry over most of EPA's decisions, the EPA banned most food uses of methyl parathion and posed restrictions on azinphos methyl use [100]. ACPA president Jay Vroom proclaimed that the groups only agreed to the settlement "because

they knew there was the threat of a food scare" [100]. Yet the actions on these two pesticides did little to mollify environmental and health groups, including Consumer's Union, who had expected a full review of the 39 OPs and claimed that most of the 3,200 pesticide decisions had "no impact on food safety" [100]. CU later argued that the EPA had simply "'cherry-picked' the biggest and ripest targets for risk-reduction" [87]. Furthermore, a lawyer for the NRDC argued that the burden of proof should have been on the pesticide manufacturers to prove that their products were safe, claiming, "There is significant evidence that much lower levels of these chemicals at critical levels of development can cause lifelong deficits, potentially" [100]. Later that day, the NRDC filed a lawsuit against the EPA maintaining that the agency failed to follow the congressionally mandated schedule for the FQPA review. In an editorial several days later, the *New York Times* acknowledged that the EPA faced a difficult scientific and regulatory task, but agreed that " the environmental groups are surely justified in complaining that the E.P.A.'s pace has been sluggish" [101].

Though controversial, the first round of decisions somewhat quieted the public angst over the OPs, and much of the future wrangling took place in the courtroom and within the agency. The Farm Bureau and the ACPA made one last legislative effort by supporting the introduction of two bills by House Republicans aimed at overturning sections of the FQPA. Richard Pombo's (R-CA) "Regulatory Fairness and Openness Act" nearly paralyzed the pesticide review by imposing strict data requirements, and at one point gained over 200 supporters, but ultimately never underwent a full vote [102]. In response to the NRDC's lawsuit in 1999, the ACPA and Farm Bureau, among twenty plaintiffs, filed a lawsuit of their own, attempting to force the EPA to use similar strict

data requirements [102]. In a move that surprised both environmental and industry groups, the animal-rights organization People for the Ethical Treatment of Animals (PETA) also sued the EPA, arguing that DNT testing was not scientifically validated and resulted in the unnecessary deaths of at least 1,200 animals per study (PETA later started a public relations campaign calling the NRDC and the World Wildlife Fund "Mean Greenies" due to their support of the DNT testing) [103].

Chlorpyrifos: Effects Observed 2000-2001

> *Maybe the EPA will do the right thing.... Maybe it won't kill asthmatic children by banning potent roach-killing sprays. But a lot of little critters have their antennae crossed hoping otherwise.*
>
> *-Michael Fumento, April 2, 1998, Editorial in the Wall Street Journal* [78]
>
> *There is simply no credible scientific evidence that Dursban products harm people or the environment when used properly.... No significant adverse health effects will likely result from exposures to Dursban, even at levels substantially above those expected to occur when applied at label rates.*
>
> *-Advertising Claims by Dow AgroSciences between 1995-2003 regarding Chlorpyrifos (Dursban)* [104]
>
> *Chlorpyrifos is one of the great success stories in pest control today.*
>
> *-Dow AgroSciences Website, March 2007*

A section on chlorpyrifos, one of the most commonly used OPs at over 30 million pounds per year, warrants attention not as an example of corporate malfeasance but for two reasons of historical significance. Firstly, scientists have studied the DNT effects of this organophosphate more thoroughly than any other pesticide, largely due to work of the Duke toxicology department and one scientist in particular, Theodore Slotkin. Secondly, chlorpyrifos remains the only major OP for which the EPA has incorporated

developmental neurotoxicity data into its review process, largely due to Slotkin's studies. I include here an appropriate mention of the evolution of our understanding of chlorpyrifos's developmental neurotoxicity because it constituted the leading edge of knowledge for all OPs.

In the late 1980s and early 1990s, toxicologists regarded chlorpyrifos as safer than most other organophosphates. It was thought that chlorpyrifos only caused persistent neurological problems, similar to those seen from "ginger jake," at exposure levels greater than those required for frank poisoning, and thus greater than established "safe" levels [105]. However new studies illustrated increased neurological susceptibility in developing animals as compared to developed animals, leading scientists to question the safety of "safe" exposure levels. Regulators responded to this concern by measuring cholinesterase levels, which they believed would straightforwardly monitor exposure consequences [70, 95, 106]. From a regulatory perspective, good measurements lead to safe tolerance levels.

In the mid-1990s, scientist found evidence that nicotine could act as a teratogen, working to "mis-wire" the brain by acting on neurotransmitters important for the complex process of nervous system formation [105]. Building on these discoveries, in the late 1990s Duke scientists revealed that chlorpyrifos's actions could occur entirely separately from, and at lower levels than, its effects on cholinesterase. Regulators realized a need to reform the conclusion that monitoring cholinesterase levels in animal models was sufficient for setting safe chlorpyrifos exposure levels. By the time the EPA issued its ruling on chlorpyrifos, research on the subject had mushroomed, and over the next few years scientists elucidated chlorpyrifos's toxic effects down to the molecular level [105].

In 1999, amidst the frenzied debate over agricultural OP use and food tolerances, the EPA quietly increased its focus on indoor organophosphate exposures. For years environmental groups had preached against the residential use of the chlorpyrifos (manufactured by Dow AgroSciences, marketed under the trade names Dursban and Lorsban, and present in products including Raid sprays and Black Flag Roach and Insect Killer), particularly when young children were present. These groups pointed to the studies on developmental neurotoxicity as well as anecdotal reports of poisoning, which skeptics dismissed as "junk science" [107]. Physician and toxicologist Ronald Gots argued, "activists are trying to build a case against the vast body of existing science showing chlorpyrifos is safe," and declared the activists' claims scientifically baseless [107]. The next year a study published in *Environmental Health Perspectives* showed that chlorpyrifos was not only persistent and long-lasting indoors, but was present at much higher concentrations than previously expected [108]. Simultaneously, Duke researchers continued to find chlorpyrifos-induced developmental neurotoxicity at progressively lower concentrations and through previously unexpected mechanisms [96, 109]. Perhaps a major turning point in focusing the EPA's attention was a 1999 study showing that out of all the counties in New York State the heaviest pesticide use occurred in the urban boroughs of Manhattan and Brooklyn, rather than in the agricultural counties upstate [110].

In 2000 the EPA, upon reviewing the scientific evidence, decided that indoor OP uses posed a serious health hazard to children and began negotiating with the pesticide maker Dow AgroSciences for the removal of chlorpyrifos from the indoor pesticide market. Many conservative groups cried foul and disputed the EPA's decision. One such group, the Heartland Institute (HI), employed the strategy of touting a pesticide's health

benefits while minimizing its risks. The OPs, they claimed, were "extremely effective in controlling cockroaches, whose feces, the World Health Organization says, are a principle cause of asthma" [111]. The HI incorrectly proclaimed that "no deaths or even illnesses have been linked to their use," [111]. Finally, in June 2000, and despite the protestations, the EPA announced an accord that would eliminate all indoor and several agricultural uses—about 50% of the 20 million pound market—of chlorpyrifos and diazinon, a similar high risk OP [112].

Environmental and health groups hailed the June 2000 decision as a major victory, while the Vice President of Dow AgroSciences, Elin Miller, refused to acknowledge the pesticide's risks. Speaking on behalf of the company, Miller stated, "The rules have changed, but the safety of chlorpyrifos hasn't" [112]. Notably, in 2003, New York State Attorney General Eliot Spitzer forced a $2 million settlement with Dow AgroSciences for making false advertising statements about chlorpyrifos's safety. Spitzer's office called the settlement "the largest enforcement penalty ever obtained in a pesticide case" [104]. According to the press release, Spitzer sued the company for "repeatedly violating a 1994 agreement," in which Dow "agreed to stop making claims that its products were 'safe,'" [104]. Yet as late as 2003, Dow's website stated that the proper use of chlorpyrifos yielded "wide margins of safety for both adults and children" [104].

As late as 2007, Dow AgroSciences carefully noted on its website that the 2000 agreement was not in fact a ban. This distinction remains relevant as the EPA's pesticide reviews often carry significant weight in the pesticide regulation of other countries. Dow AgroSciences's website for Latin America, where many countries still use chlorpyrifos

residentially, presented the EPA's 2000 action as the result of a simple bureaucratic maneuver. Under the FQPA, the website claimed, EPA "applied standards far more restrictive than those historically established by the scientific community and other competent regulatory authorities around the world" [113]. "The rules changed," they contended, "but the studies done with chlorpyrifos have not changed," and trumpeted that the pesticide "has not been banned as reported in many popular press articles" [113]. In the toxicology section, the company maintained that the only chronic toxic effects from chlorpyrifos were "those associated with the inhibition of cholinesterase enzymes," and that even at doses thirty times higher than the NOAEL, "no adverse effects were observed during [a] two-year test period" [113]. A contemporaneous comprehensive review of chlorpyrifos toxicology strongly contradicted this finding, stating, "the delayed-onset deficits after chlorpyrifos exposure are evoked at doses either below the threshold for detectable cholinesterase inhibition" [20]. This careful maneuvering allowed Dow AgroSciences to continue to manufacture and ship Dursban overseas after agreeing to eliminate domestic (in both senses of the word) use.

At the close of the 10-year FQPA pesticide review process, the 2000 agreement on residential chlorpyrifos use, according to many physicians and environmentalists, stood as a critical decision in reducing OP risks to infants and children. This belief, in large part, stemmed from the results of a series of scientific studies, published between 2004 and 2006 by a group at Columbia University's Center for Children's Environmental Health. Beginning in 1997, Columbia researchers measured the levels of chlorpyrifos present in the umbilical cord blood of over 200 newborn babies in Harlem and the South Bronx (areas with very high levels of indoor chlorpyrifos use) and followed them over

several years. They found that infants with higher levels of chlorpyrifos had lower birth weights, often a marker of brain development, and worse scores on a number of neuro-developmental tests [114, 115]. They also found that infants born after the 2000-2001 phase-out of the pesticide had significantly lower levels of chlorpyrifos in their bloodstream and similarly better outcomes. These epidemiological studies, the most difficult type in pesticide inquiry, received widespread media coverage and convinced many regulators of the ban's effectiveness [116].

Cumulative Assessment

> *I am pleased that the Agriculture Committee has placed the public health concerns of our children and elderly above those of the radical and extreme, inside-the-beltway fundraising groups who parade around as environmental or public safety special interest groups.*
>
> -Rep. Richard Pombo (R-CA), August 2000, on his proposed "Regulatory Fairness and Openness Act" [117]

By late 2000, despite the EPA's action on several individual organophosphates including chlorpyrifos, methyl parathion, and azinphos methyl, environmental groups like the NRDC and EWG continued to decry the slow pace of OP review. The ACPA and the Farm Bureau, meanwhile, expressed some measure of relief that the FQPA process had not been as stringent as they had feared in eliminating pesticide uses—an April 2000 report by the General Accounting Office found that the EPA had toughened or eliminated only 13 percent of the 3,471 tolerances examined to date [118]. Both sides, however, waited in anticipation of EPA's final decisions on the remaining OPs and on the outcome of the controversial cumulative risk assessment (CRA). As mandated by the FQPA, the EPA had to issue tolerances not only on the individual OPs and their health hazards, but

also on the group as a whole, considering the additive, or cumulative, effects on the nervous system. Environmental groups saw the CRA as a prime opportunity to cancel the most dangerous OP uses, while industry groups made efforts to forestall the process and weaken implementation.

Both the ACPA and the Farm Bureau again, in late 2000, pushed for legislation in Congress to weaken the FQPA. They supported the Regulatory Fairness and Openness Act introduced by Rep. Richard Pombo (R-CA), which Pombo described as directing the "EPA to use sound science, not the whim of the Washington bureaucracy, to implement the FQPA" [117]. The EPA, in response, publicly warned that Pombo's bill could delay implementation of the FQPA's public health measures and "effectively defeat" the law's deadlines [117]. In November 2000 industry groups scored a minor victory when a district court rejected a plea by the NRDC and the EPA to dismiss an industry lawsuit against the agency that the EPA said would make the pesticide reassessment process unworkable. The suit alleged that EPA had used faulty scientific methods in its review of the OPs, and aimed to limit what health data the agency could consider when reviewing pesticides [119]. Another event that month, the election of George W. Bush as president, bolstered the pesticide industry's confidence and later proved far more important to pesticide policy than the court's decision.

In January of the following year, industry groups became infuriated after the EPA settled an NRDC-led lawsuit out of court in what *Chemical Week* called an "11th-hour deal" [120]. NRDC's lawsuit, filed in 1999, charged that the EPA had missed deadlines for review decisions on pesticides, including the OPs. The settlement, which NRDC senior attorney Erik Olson remarked "had been in the works for years," included a firm

timetable for the remaining OPs and a May 31st, 2002 deadline for the organophosphate cumulative risk assessment [121]. The ACPA and other industry groups, who had hoped to win concessions with their own court case, complained that the settlement was a political attempt to "tie the hands" of the incoming Bush Administration by setting "new reassessment schedules that are very arbitrary" [121]. Farm Bureau president Bob Stallman claimed that industry groups were surprised by the announcement, grumbling "we should have been more cynical and realized that a decision this far-reaching would be made on the Clinton Administration's last day in office" [121]. In the following months, new Bush-appointed EPA administrator Christine Todd Whitman tried to extricate the agency from the settlement. However, due to what Whitman termed "limited flexibility" in the ruling, the Bush Administration finally acceded, though adding an industry concession that created more room for "public comment" on EPA decisions [122].

With a new timetable in place, the EPA had just over a year to complete the CRA for the OPs, which had been under development for several years (and, according to Consumer's Union, subject to "protracted debate and interminable review") [123]. The NRDC and CU had hoped that the EPA would now incorporate the incoming developmental neurotoxicity data earlier requested by the agency, or at least use the 10-X factor where knowledge gaps existed, yet the final debates centered around older, more narrow, issues. Similar to other post-FQPA deliberations, many of the final meetings focused on varying estimates for OP exposure levels. On the health effects side, the EPA had already disappointed environmental and health groups with the decision to consider the cumulative effects of the anti-cholinesterase carbamates separately from those of the

organophosphates, despite their shared mechanism. In 2001, despite evidence that many OPs caused neurotoxic effects at levels below cholinesterase-inhibition, the agency decided to focus the risk assessment on cholinesterase levels, largely because these were the most easily measured outcomes, when setting allowable OP exposures. CU and the World Wildlife Fund (WWF) questioned the EPA's "methodology that a 10 percent depression of brain cholinesterase activity is of no biological significance" given the "strong evidence that OPs are developmental neurotoxins" [123]. These same groups, however, praised the EPA for the "enormous amount of work invested" in the CRA and remained largely supportive of the review [123].

EPA's chief administrator Stephen Johnson hailed the May 2002 release of the CRA as "good news for American consumers," and claimed that its "conclusions supported a high level of confidence in the safety of the food supply" [124]. The agency boasted that the report included "consideration of the FQPA safety factor," yet environmental groups asserted that the "consideration" given was far from sufficient [124]. One year prior to the report, the EPA retained the full 10-X factor, or a lesser 3-X factor, in only 16% of OP decisions. EPA cited a lack of DNT data as the reason for maintaining the 10-X factor in three-quarters of these decisions [87]. Given the growth of peer-reviewed literature and the EPA's dearth of DNT studies, CU and NRDC anticipated that the EPA would extend the 10-X uncertainty factor under the CRA to many more OPs. Instead the CRA removed the 3-X factor on four OPs based on limited data, and applied only a 3-X factor on several others [125]. The EPA failed to apply the 10-X factor in all cases where data was lacking, a critical tenet of the FQPA.

In their 2002 comments to the EPA, environmental groups claimed that the

agency had “flouted the plain language of the FQPA and Congress’ clear intent” [126]. The following month a majority of participants on the EPA’s own Scientific Advisory Panel concurred with this idea, concluding “that the confidence with the available data was not sufficient to assure adequate protection with less than the 10x FQPA safety factor” [127]. This is a point that bears repeating. Nearly a decade after the publication of the 1993 NAS report, and six years after the FQPA’s passage, a majority of the EPA’s advisors agreed that the agency had not sufficiently addressed developmental effects or fully applied the 10-X factor, both explicit recommendations of the NAS report and the FQPA.

The 2002 Cumulative Risk Assessment essentially marked the end of the review process for the organophosphates. Industry groups, having suffered a number of OP losses under the FQPA—but feeling more secure under the Bush Administration—remained relatively satisfied with the report’s outcome and largely abandoned their political and legal offensives. Environmental groups, on the other hand, expressed frustration with the result, and pointed to the EPA’s failure to fully apply the 10-X safety factor or consider adequate DNT studies. The NRDC sued the EPA, again, over this issue, but was ultimately unsuccessful. The disappointment ran deep for environmental health physicians, who saw the OPs as the test case for the FQPA and as an important—and hazardous—group of its own. Environmental groups quietly shifted their focus away from OPs, developmental neurotoxicity, and the 10-X factor after 2002; however, scientists within the EPA increasingly expressed dissatisfaction with the OP results. By 2006 many EPA toxicologists and risk assessors felt that political pressure as much as science had driven the decisions on the OPs, and began to speak out against earlier

conclusions.

Discord at the EPA

> *Our colleagues in the Pesticide Program feel besieged by political pressure exerted by Agency officials perceived to be too closely aligned with the pesticide industry and former EPA officials now representing the pesticide and agricultural community.... Equally alarming is the belief among managers in the Pesticide and Toxics Programs that regulatory decisions should only be made after reaching full consensus with the regulated pesticide and chemicals industy.*
>
> *-Local Presidents of EPA Unions, May 24, 2006, Letter to Administrator Stephen Johnson* [128]

In the three years following the 2002 OP cumulative risk assessment the EPA gave little public attention to organophosphates, apart from a continued conflict over the contentious issue of human testing. During this time toxicologists at Duke and elsewhere continued to understand startling mechanisms of organophosphate induced neurodevelopmental damage [129-131]. Even within the EPA scientists became increasingly concerned that the OP reregistration had not gone far enough in protecting against developmental neurotoxicity. Yet the EPA offered no public recognition of the latest research findings or of internal concerns until, ultimately, the release of an internal audit report.

In January 2006 the Office of Inspector General (OIG), EPA's self-auditing department, released a public report. The OIG found many faults with EPA's actions on the FQPA stating, "EPA's required testing does not include sufficient evaluation of behavior, learning, or memory in developing animals" and "there is no standard evaluation procedure for interpreting results from developmental neurotoxicity tests" [132].

Regarding the requested DNT data from manufacturers, “no summaries have been released or conclusions drawn” [132]. Furthermore, the OIG concluded that the EPA’s core testing guidelines themselves had “no requirement for specific testing of developmental neurotoxicity in developing animals” [132]. Ten years after the FQPA mandated that EPA assess effects on immature organisms, OIG found “all but two core toxicity tests... for food use pesticides are performed in adult animals, including the only test of metabolism” [132]. These gaps led the OIG to “fear the loss of public confidence in EPA’s commitment to protect infants and children from developmental hazards” [132].

The Inspector General’s report leant credence to those within the agency concerned with the lack of DNT data in the OP review. The report helped kindle an open letter, dated May 24, 2006, to EPA Administrator Stephen Johnson, which put these concerns on a national stage [128]. In what the *Wall Street Journal* called an “unprecedented and professional rebuke to Mr. Johnson,” union leaders representing over 9,000 scientists and other employees at the EPA asserted that their “colleagues in the Pesticide Program [felt] besieged by political pressure exerted by Agency officials perceived to be too closely aligned with the pesticide industry” [128, 133]. They claimed that the “integrity of the science upon which agency decisions are based [had] been compromised” in a “rush to judgment” to meet the final August 3rd FQPA deadline, and echoed the Inspector General’s concerns about the EPA’s neglect of developmental neurotoxicity testing [128]. The union leaders finally urged the EPA to “adhere to principles of scientific integrity and employ the precautionary approach intended by the FQPA” by retaining the 10-X safety factor [128]. Jay Vroom, CropLife America President (formerly ACPA), responded to this letter saying, “It is very difficult to place any

credibility on [this] assertion of political pressure," given "the transparency and oversight being accorded to the EPA's activities on pesticide reassessment" [134]. Vroom speculated that environmental groups may have been "anticipating scientific findings not to their liking and [were] setting the stage for future disagreements and potential litigation" [134].

In the short-term the letter had little effect. In August 2006 the EPA released the third and final FQPA report on the OPs. EPA Administrator Stephen Johnson proclaimed, "Whether planting crops, de-bugging a home, working in the garden or just sitting down at the dinner table, Americans can now be assured the pesticides used in the U.S. meet the highest health standards in the world" [135]. Still many within the EPA remained skeptical of the review, particularly over the lack of DNT testing. EPA senior scientist William Hirzy observed that EPA officials "think they dealt with our concerns that we raised in the letter, and we don't think that they have" [136]. Outside the EPA anti-pesticide groups voiced stronger criticism of the review. Pesticide Action Network senior scientist Margaret Reeves declared, "the OP decision, I think, is a bad one" [136]. Industry groups, on the other hand, gave guarded praise for the final OP reports. Ray McAllister of CropLife America claimed that the OPs had been "thoroughly investigated" and noted the dozens of DNT studies reported to the EPA since 1999 [136]. "If anything," he claimed, "the approach EPA has taken has been more conservative, more protective, than perhaps they actually need to be" [136].

Thus ends the decade-long organophosphate FQPA review, one of the most recent, and public, chapters in the long and controversial history of pesticides. Neither industrial nor environmental groups remained entirely contented with the outcome, but

nearly all could agree that, on balance, the FQPA improved pesticide safety and lowered risks to children. Perhaps some of the disappointment experienced by the environmentalists at the end of this process stemmed from the high expectations initially set by the FQPA, namely its 10-X and "reasonable certainty of no harm" provisions. Though the EPA did not implement the law in its entirety, the FQPA did radically change the terms of the pesticide debate. The FQPA forced all parties to adjust their outlooks by mandating the EPA to focus exclusively on health, risks to children, and total and cumulative risks of organophosphate pesticides.

Conclusion

Pesticides are the iconic toxicants of the twentieth century—useful yet ubiquitous, effective yet dangerous. The organophosphates were born as weapons of war, but refined and studied by pharmacologists like pharmaceuticals. The pesticide armamentarium is as diverse as the U.S. Pharmacopoeia. To fully understand pesticides' adverse effects, one must appreciate toxicology, teratology, carcinogenicity, neurodevelopment, laboratory limitations, skin and respiratory hazards, indoor and outdoor air dangers, drinking water and aquatic risks, food contamination, and worker and consumer threats. As always economics pervades all discussions, and legal and legislative decisions frame the debate. Only with an appreciation for this complexity and an understanding of these varied yet relevant subjects does one reach the surface of the politics surrounding pesticides—state, national, and international—not to mention the aggressive scrutiny of the media and the vested interests.

The case of developmental neurotoxicity from organophosphates illustrates a

small, but consequential, slice of the density involved in pesticide regulation. It exemplifies the evolution of the pesticide debates over the past few decades. New measurement techniques, new toxicological studies, and new modes of thinking—largely derived from experiences with lead—allowed developmental neurotoxicity to become the primary concern for organophosphates. The EPA's failure to reasonably incorporate DNT data into the recent review process or fully implement the 10-X safety factor is largely a product of economic and political influence in the years following the FQPA, and primarily under the Bush administration. Richard Wiles, a founding member of the EWG involved in drafting the FQPA, stressed in 2007 the importance of the safety factor, calling it a "policy and legislative first" that "has now become the baseline starting point for standard setting even if it is not always applied" [137]. Though the EPA failed to fulfill the FQPA's mandate to consider all pre- and post-natal pesticide effects, this legislation drastically reframed the pesticide debate and its precautionary remained at least partially intact.

Before the FQPA, pesticide arguments centered on cost-benefit analyses in which health risks were difficult to prove and possible economic costs were readily apparent. After the FQPA the EPA could no longer explicitly consider economic factors, and the pesticide industry was forced to change its tactics as well – turning to loopholes, bargaining, and delay. The elimination of the Delaney clause, considered a victory for the food processing industry, actually worked against the pesticide manufacturers by removing the emphasis on cancer and shifting attention to other important health consequences, notably neurodevelopment. The law also moved the focus from pesticides' effects on adult males to the more vulnerable infants and children. Before the

FQPA, according to Wiles, the pesticide fights were “about average [population] risks versus cost to apple growers” [137]. The FQPA forced the EPA to ignore the economic burden and examine not just average adult risk but specific threats to children. Wiles summarized the overall change succinctly, “Now, for example, a 300 fold safety margin on a No Effects level from a developmental neurotoxicity study is considered a weak standard. That's progress” [137].

Though the FQPA review process did not extend as far as many health and environmental groups had wanted, it did achieve a number of important risk reductions on some of the most dangerous organophosphates. Perhaps most importantly this legislation eliminated nearly all indoor uses of the widely used chlorpyrifos and diazinon. The act phased out all uses of methyl and ethyl parathion, and set a schedule to eliminate all uses of azinphos methyl. In addition, the FQPA toughened tolerances and other allowable limits on many other organophosphates. If past experiences with lead, mercury, PCBs, and other neurotoxicants serve as an appropriate guide, however, we may find through further research that even these actions will prove inadequate to appropriately protect infants and children. For example, the true contribution of organophosphates to the increasing burden of neurological diseases like autism, mental retardation, Alzheimer’s and Parkinson’s remains unknown.

The case of chlorpyrifos may serve as an example of developmental neurotoxicity discovery for other OPs. Academic toxicologists studied developmental effects of chlorpyrifos more thoroughly than any other OP, and these results, far more than the EPA mandated studies, initiated the agency’s action on this insecticide. Theodore Slotkin, the world’s expert on the DNT effects of chlorpyrifos, noted in a 2004 article that his

laboratory discovered the prominent neurodevelopmental effects not because chlorpyrifos caused this “mis-wiring” more readily than other OPs, but because it was one of the only OPs studied in this manner. Slotkin propounded that a barrier existed between academic toxicology, with its focus (and funding) on discovering novel mechanisms of action, and regulatory toxicology, with its need for high volume chemical screening [105].

Slotkin was proactive in offering his concerns and recommendations for pesticide regulation to the EPA. He wrote that EPA “guidelines for developmental neurotoxicity are rapidly becoming insufficient to accommodate our increasing knowledge of the molecular, biochemical, and cellular processes that underlie brain development,” and proposed a new set of guidelines flexible enough to incorporate scientific advancements [105]. In the first of two stages, termed high-throughput screening, investigators would apply pesticides to neural cell cultures and developing lower-order organisms to identify dysfunctional cell division or differentiation. This stage would incidentally help satisfy PETA’s demand for less animal experimentation and the pesticide industry’s demand for less expensive testing technology. The proposed second stage included smaller-scale animal testing for traditional toxicology outcomes. Slotkin and many other toxicologists hoped that these two parts would help reduce many of the gaps in the current DNT testing system [105].

Despite the FQPA’s focus on infants and children, it paid relatively less attention to highly exposed populations, particularly farmworkers and their families. The law incidentally offered some increased protection to these groups by reducing or eliminating the riskiest OPs, but many poisonings still occur. Studies in the past few years have shown that children of farmworkers have much higher exposures to pesticides as

compared to their cohorts [138]. Yet a powerful new tool for protecting farmworkers and their children is beginning to mature in the form of biomonitoring, which is simply the measurement of chemicals and their metabolites in the bloodstream or urine. This tool is particularly effective for measuring chemicals like organophosphates, which have a relatively short lifespan and are difficult to detect with normal sampling techniques. The CDC now tracks the levels of over one hundred chemicals in a representative sample of Americans, determining a population average without fully interpreting the data. This information allows environmental health specialists to compare levels in individuals to the population average and to provide fairly definitive proof of increased exposures. Scientists are already correlating certain bodily concentrations of chemicals with adverse outcomes and many believe that they will find stronger associations in the future that will provide the basis for stronger legislation [139].

Integrated Pest Management (IPM) and organically grown food are two burgeoning trends that reduce exposures to neurotoxic insecticides. IPM uses biological, cultural, and physical tools, like crop rotation and cultivation of insect predators, to manage pests in a way that minimizes chemical pesticide use. Farmers grow organic food without synthetic pesticides, often using IPM or “natural” pesticides, which reduces exposures to both farmworkers and consumers. A 2003 study in Washington State showed that children consuming only organic food had dramatically lower levels of organophosphate metabolites in their urine than children eating non-organic diets. Several children in the non-organic group, while none in the organic cohort, had levels of OPs exceeding the EPA standard [140].

Complicating the pesticide question, Americans are eating increasing amounts of

imported fruits and vegetables, which are generally less regulated than those grown domestically. American pesticide manufacturers can still legally make several organophosphate insecticides that are banned in the U.S. to sell in other countries. Ironically, the banned pesticides often return to the United States in imported fruits and vegetables. Many of these exported insecticides have tragic consequences for the nations that receive them. Poisonings are common among the untrained rural farmers that use organophosphates, and intentional OP overdose is the most common method of suicide in many parts of Asia [141].

The fights over pesticides are among the most contentious in environmental health, yet past experience has shown that the concerns of today are rarely those of tomorrow. Following *Silent Spring* in 1962, growers predicted dire consequences if the government banned organochlorines, yet food shortages did not materialize in the 1970s when the EPA cancelled DDT and its brethren. Furthermore, many insects had already developed resistance to the blunt force of the OCs. Those who use and study pesticides are beginning to take a lesson from the physicians and epidemiologists who investigate antibiotic resistance. The answer to "pest" control, whether for bacteria or insects, is in the wise, judicious use of the compounds with the fewest side effects. A shrinking planet with a growing population and increased travel will present new pest challenges to both doctors and farmers. The twentieth century era of crude tools like nerve poisons surely will end, but the need to control pests will not.

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