

**Expert Report  
Frederick R. Davis, Ph.D.**

|                                                                                              |    |
|----------------------------------------------------------------------------------------------|----|
| Executive Summary .....                                                                      | 1  |
| Qualifications .....                                                                         | 1  |
| Pure Food and Drug Act 1906 .....                                                            | 3  |
| Insecticide Act 1910.....                                                                    | 4  |
| Calculating the Median Lethal Dose (LD <sub>50</sub> ).....                                  | 5  |
| The Federal Food, Drug, and Cosmetic Act (FFDCA) – 1938.....                                 | 6  |
| Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) - 1947 .....                     | 7  |
| Chemicals in Food Products Hearings: The Delaney Clause and the Miller Amendment .....       | 8  |
| Federal Environmental Pesticide Control Act (FEPCA) - 1972 .....                             | 10 |
| Federal Pesticide Act of 1978 .....                                                          | 13 |
| The Red Book (1982).....                                                                     | 13 |
| Food Quality Protection Act (1996).....                                                      | 15 |
| Industrial Bio-Test Laboratories, Chevron Chemical Company, and Paraquat Toxicity Data ..... | 15 |
| Paraquat not Tested for Neurotoxicity .....                                                  | 18 |
| Failures to Fully Disclose Risks to the EPA .....                                            | 19 |
| Improper Influence by the Manufacturers on the EPA .....                                     | 20 |
| Paraquat Widely Banned.....                                                                  | 21 |
| References Cited .....                                                                       | 23 |

## Executive Summary

In this report, I review the history of federal regulation of pesticides from the Pure Food and Drug Act of 1906 to the Food Quality Protection Act of 1996. I also review the development of techniques in toxicology, such as the derivation of the Median Lethal Dose (LD<sub>50</sub>). I relate the wider story of the legislative and scientific framework around pesticides to Paraquat.

## Qualifications

I am Professor and Head of the Department of History at Purdue University. I also hold the R. Mark Lubbers Chair in the History of Science. I have been studying the history of the science of toxicology and the development of chemical pesticides for more than two decades. In 2014, I published *Banned: A History of Pesticides and the Science of Toxicology* with Yale University

Press. This book was based on my dissertation at Yale University, which I completed in 2001. *Banned* examined the evolution of chemical pesticides and the development of the medico scientific discipline of Toxicology to interpret risks of chemicals to humans, wildlife, and ecosystems. I trace how legislation and regulation emerged in the face of rapidly changing risks. In addition to *Banned*, I have published ten articles on the history of pesticides and toxicology. I have served on editorial boards for *ISIS: An International Review devoted to the History of Science and Civilization*, *Environmental History*, *Agricultural History*, and the *Journal of the History of Biology*. My research has been funded by grants from the National Library of Medicine / National Institutes of Health, the National Science Foundation, and the Fulbright Senior Scholar Program.

I received my Ph.D. in the History of Science and Medicine at Yale University in 2001 (Dissertation: “Pesticides and Toxicology: Episodes in the Evolution of Environmental Risk Assessment (1937-1997).” I also received an M.Phil. and an M.A. at Yale as well as an M.S. in Biology at Southern Connecticut State University and an M.A. in the History of Science at the University of Florida. I received my A.B. in History and Science *Magna cum laude* from Harvard College (Harvard University). Before I moved to Purdue University in 2016, I was a professor at Florida State University for fifteen years and the Rochester Institute of Technology for one year. I also spent one academic year (2016-17) at the Chinese University of Hong Kong as a Fulbright Senior Scholar.

My opinions and conclusions are held to a reasonable degree of professional certainty and are based on my education, training, research, and experience. I have not testified in the last four years. I charge \$500.00 an hour for document review and report drafting. I charge \$650.00 an hour for deposition and trial testimony. My fee is not contingent on the outcome of this case. I reserve the right to update and add to my opinions if and when additional information becomes available to me.

#### **History of Pesticide Regulation and Registration in the U.S.**

- PFDA – 1906
- Insecticide Act – 1910
- Calculating the Median Lethal Dose (LD<sub>50</sub>)
- FFDCA – 1938
- FIFRA-1947
- Miller Amendment and The Delaney Clause
- FEPCA – 1972
- The IBT Scandal, Chevron, and Paraquat
- Federal Pesticide Act 1978
- The Red Book*
- FQPA - 1996

## Pure Food and Drug Act 1906

The Pure Food and Drug Act finally passed in June of 1906. During the prior twenty years, Congress had debated food and drug safety numerous times, but legislation failed to emerge. Meanwhile, much of the nation's meat supply was produced in the Chicago Stockyards. The conditions in the stockyards attracted international attention when the British medical journal *Lancet* sent a public health physician to report on the of meatpacking conditions there. In three separate papers, the British doctor recorded his horror at the conditions of the stockyards, which were among the largest in the world. However, technical reports failed to inspire reform efforts or even concern. An early consumer advocate, Harvey Washington Wiley, argued for the precautionary principle: "Only precaution could protect the public from harm; waiting to see whether a particular chemical contaminant in food might be harmful was unethical, for it would turn America into a nation of guinea pigs" (Langston).

Nevertheless, decisive action was delayed until Upton Sinclair published *The Jungle* in February 1906. He was hoping to draw attention to the plight of immigrant workers who faced abysmal working conditions in the stockyards (Sinclair). But Sinclair's descriptions of conditions in the meatpacking plants horrified readers including legislators:

It was only when the whole ham was spoiled that it came into the department of Elzbieta. Cut up by the two-thousand-revolutions-a-minute flyers, and mixed with half a ton of other meat, no odor that ever was in a ham could make any difference. There was never the least attention paid to what was cut up for sausage; there would come all the back from Europe old sausage that had been rejected, and that was mould and white—it would be dosed with borax and glycerine, and dumped into the hoppers, and made over again for home consumption. There would be meat that had tumbled out on the floor, in the dirt, and sawdust, where the workers had tramped and spit uncounted billions of consumption germs. There would be meat stored in great piles in rooms; and the water from leaky roofs would drip over it, and thousands of rats would race about on it. It was too dark in these storage places to see well, but a man could run his hand over these piles of meat and sweep off handfuls of the dried dung of rats. These rats were nuisances, and the packers would put poisoned bread out for them; they would die, and then rats, bread, and meat would go into the hoppers together. This is no fairy story and no joke; the meat would be shoveled into carts, and the man who did the shoveling would not trouble to lift out a rat even when he saw one—there were things that went into a sausage in comparison with which a poisoned rat was a tidbit (Sinclair).

Congressional hearings and negotiations ensued with renewed intensity. In just four months (in June of 1906), the President signed the Pure Food and Drug Act into law. It mandated accurate labels for food and drugs. It also prohibited interstate transport of unlawful foods or drugs. Thus, the PFDA set the standard for food and drug regulation: accurate labeling, a standard that would remain in effect for decades.

## Insecticide Act 1910

Once the PFDA established labeling standards for drugs and foods in the U.S. in 1906, prospects for comparable standards for insecticides (and fungicides) began to look very promising. E. Dwight Sanderson reported that one of the nation's largest insecticide manufacturers agreed to include an analysis of its goods on all labels. As the director and entomologist of the New Hampshire Experiment Station and the head of the Standing Committee on Proprietary Insecticides of the Association of Economic Entomologists, Sanderson interpreted the agreement as a promising sign that the insecticides industry would support his committee's resolution for national labeling legislation for insecticides and fungicides. (Whitaker). Harvey Wiley, director of the Bureau of Chemistry and a staunch advocate for the regulation of foods and drugs, encouraged Sanderson to lobby Congress for such legislation for three reasons: the PFDA did not extend to insecticides, an amendment to the PFDA was not feasible, and labeling of insecticides was critically important.

When compared to the tortuous path of the food and drug act, passage of the insecticide act was both speedier and more direct. The passage of the Insecticide Act in April 1910 confirmed Sanderson's impression that the insecticide industry was ready for regulation. Historian Adelynn Whitaker argued that the quick passage of Insecticide Act hinged on industry acceptance, but insecticides producers witnessed how the food and drug act benefited responsible and reliable producers of food and drugs, whereas producers of adulterated goods were forced out of the market (Whitaker).

Just as the PFDA set labeling standards for foods and drugs, the Insecticide Act of 1910 established similar standards for insecticides. The manufacture and sale of adulterated and misbranded insecticides and fungicides in interstate commerce became illegal under the insecticide law. It codified legislative standards for insecticides in general and specifically the two insecticides that were most commonly used in the United States: Lead Arsenate and Paris Green. Regulators expected specific standards to reduce problems with enforcement, which had posed difficulties for the USDA. Enforcement of the federal Insecticide Act fell to the Insecticide and Fungicide Board within the Bureau of Chemistry. Early in the act's history, few if any noted the potential conflict of interest, but by the mid-1920s, the USDA's dual role as protector of both farmers and consumers garnered criticism, particularly as the problem of pesticide residues on produce became a matter for regulatory concern.

By 1930 insecticide use in the United States had exploded to unprecedented levels. Farmers sprayed nearly sixty million pounds (27,215,542.2 kg) of the two most popular insecticides (calcium arsenate and lead arsenate) on crops in 1929. Only rarely did spray residues result in cases of acute poisoning and death, but scientists and physicians began to link common ailments like eczema and stomach upset with chronic arsenic and lead toxicity. International regulation of spray residues on fruit imported from the United States prompted review and revision of standards, but levels remained much higher for fruit sold in the U.S. Even Kallet and Schlink's exposé (*100,000,000 Guinea Pigs*) provoked a relatively minor protest. Most Americans remained complacent, assuming that the 1906 PFDA protected them from contaminated food and drugs, and farmers relied on the Insecticide Act of 1910 to keep insecticides free from adulterants. Nevertheless, by 1933 regulators had received executive approval to revise the pure food law.

Tragically, an epidemic of poisonings failed to accelerate the legislative process (Carpenter, Davis).

#### Calculating the Median Lethal Dose (LD<sub>50</sub>)

The FDA was established in 1927, when the activities of the Bureau of Chemistry within the USDA became distinct from agricultural chemistry and the work of the department as a whole. Regulators and regulatory chemists were moved to a separate agency called the Food, Drug, and Insecticide Administration (later, the FDA). However, jurisdiction for the Federal Insecticide Act remained under the USDA. This move, noted historian Christopher Bosso, separated regulatory activities on behalf of consumers from those on behalf of farmers (Bosso). The first commissioner of the FDA, Walter Campbell was determined to examine the toxicology of lead and arsenic in response to the widespread use of these chemicals as agricultural insecticides.

The FDA mobilized its field scientists against Elixir Sulfanilamide. Through the new Division of Pharmacology it could also respond through laboratory analysis. In reviewing the existing literature, Edwin Laug and the other FDA toxicologists realized that no one had developed a method for comparing the toxicity of one substance to another. Although Laug and others suspected that diethylene glycol was the cause of the many deaths associated with Elixir Sulfanilamide, they had to develop an approach that would confirm their suspicions statistically. To do this, the FDA toxicologists were assisted by the ground- breaking research of Chester I. Bliss, who was brought to the FDA as a part-time consultant by Herbert O. Calvery. Bliss had studied with R. A. Fisher, the great English biostatistician who developed and promoted the use of statistics in biology.

Bliss had published a seminal paper, “The Calculation of the Dosage- Mortality Curve,” in which he demonstrated the sigmoid character of the typical dosage-mortality curve as established by numerous toxicological studies of a large number of organisms by many biologists. Acknowledging his debt to R. A. Fisher and the trends in biostatistics Fisher inspired, Bliss selected his procedures on the basis of their statistical accuracy and efficiency. Bliss intended to present his techniques for calculating the transformed dosage-mortality curve in sufficient detail so that biologists with limited knowledge of statistics could use them. The value of the dosage-mortality curve to biologists in general, and toxicologists in particular, arose from its ability to describe the variation in susceptibility between individuals of a population. In line with the theory that any given population would show a range of susceptibilities to any given toxin, Bliss demonstrated that mortality could be plotted against dose in a way that would indicate what percentage of any given population would be killed by a particular dose. This experimental technique could determine the precise minimum lethal dose for each organism, since a dosage above minimum effectively killed susceptible individuals. Bliss recommended exposing a series of sample groups of organisms to graduated doses and recording the percentage killed for each sample group. When Bliss plotted this data, it resulted in a sigmoid curve (exactly as predicted). (Bliss).

Bliss’s paper appeared in 1935, but the FDA pharmacologists were already familiar with his work, since he had worked in their laboratory. The dosage-mortality curve provided an excellent method

to evaluate the toxicity of a given chemical. Laug and his colleagues in the Division of Pharmacology were among the first to apply Bliss's method to an actual case when they evaluated the toxicology of glycols and derivatives in response to the Elixir Sulfanilamide disaster. Prior to this study, toxicologists had estimated the doses that were lethal to 10 percent, 50 percent, and 90 percent of a given population, but the results were unsatisfactory, particularly when toxicologists used such data to interpolate a sigmoid curve through a number of points (Laug et al.).

Laug and the FDA pharmacologists used Bliss's method to calculate and plot the dose-mortality curve for rats, mice, and guinea pigs. They determined that the most useful parameter was the lethal dose for 50 percent of the population ( $LD_{50}$ ), as this value required the fewest animals for calculation (a minimum of 10). In contrast, arriving at the same level of precision for 99 percent deaths required at least 103 animals. Moreover, Laug and his team calculated standard errors for the  $LD_{50}$  and found they could determine the dosage at which 50 percent of the population would be killed in nineteen out of twenty experiments (Laug et al.).

Citing the studies of E.M.K. Geiling and others at the University of Chicago, Laug reflected on the importance and probable significance of his team's findings for humans. Although the FDA researchers had confirmed the findings of Geiling and others, Laug advised restraint in applying the results to humans: "It seems proper at this point to reemphasize the inadvisability of attempts to interpret experimental data on laboratory animals directly in terms of man. It is entirely too dangerous. The present investigation confirms again the wide variations that may occur between species" (Laug et al.).

Although they presented the derivation of  $LD_{50}$  as a valuable new tool in toxicology, the FDA researchers acknowledged that neither acute nor chronic toxicity gave a complete picture, and scientists should assess both dimensions of toxicology. They argued for establishing the most complete toxicological profile possible. Ideally, such a profile would include both acute and chronic toxicity studies as well as pathological evaluations (Laug et al.).

A small group of FDA toxicologists in the Division of Pharmacology transformed the field of toxicology. More than any other single procedure, the Median Lethal Dose ( $LD_{50}$ ) became the benchmark in most initial studies of toxicity for pharmaceuticals and environmental chemicals. Note: to this day, there are thousands of chemicals for which there is just one known parameter of toxicity, and that is the  $LD_{50}$ .

#### The Federal Food, Drug, and Cosmetic Act (FFDCA) – 1938

High profile exposure cases prompted Congress to reopen its consideration of revising the PFDA. Although arsenic and lead spray residues and the ginger Jake paralysis epidemic affected thousands of lives and caught the attention of regulators and consumer advocates, it was the Elixir Sulfanilamide tragedy that ultimately set the stage for the development of a scientific understanding of environmental risk as posed by pesticides. Discontinuation of congressional appropriations restricted the FDA from the study of lead and arsenic insecticides, but this shift proved to be inspirational. The Division of Pharmacology at the FDA developed the  $LD_{50}$  in order to determine the toxicity of glycols and derivatives. Meanwhile, at the University of Chicago, E.

M. K. Geiling developed a broad-based approach to the toxicology of new and unfamiliar chemicals. The Division of Pharmacology at the FDA and the Department of Pharmacology at the University of Chicago served as centers for toxicological research during World War II. The research programs at the two institutions diverged after the Elixir Sulfanilamide tragedy, but they would converge in time. In addition, the study of industrial disease had developed as researchers studied workers in lead factories. This research led to the establishment of in-house toxicology laboratories at DuPont, Dow, and Union Carbide. Meanwhile, partially in response to consumer advocacy and partially in response to the Elixir Sulfanilamide tragedy, federal legislators significantly revised the PFDA to produce the Food, Drugs, and Cosmetics Act of 1938, which defined pesticides regulation for several decades. The FFDCA expanded the FDA's authority in regulating insecticides but failed to provide a provision for licensing.

#### Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) - 1947

The Federal Insecticide, Fungicide, and Rodenticide Act, signed into law in 1947, dictated the licensing of the so-called economic poisons prior to their sale in interstate or international commerce. The law also stipulated that prominent warning labels detailing instructions for use be included on highly toxic pesticides. Furthermore, FIFRA required manufacturers to color powdered insecticides to prevent confusion with other household products, for example, flour, sugar, baking soda, and salt. Historian Adelynn Whitaker emphasized that FIFRA assured consumers of quality pesticides while protecting them from accidental poisonings (Whitaker).

Registration required manufacturers to test insecticides to determine efficacy before marketing their products. Yet public health officials were disappointed that FIFRA's registration clause did not reinforce the FFDCA and control pesticide residues. In his critique of an earlier version of the bill, Paul A. Neal of the PHS recommended a consideration of public health aspects and called for coordinating toxicity testing between PHS, FDA, and USDA (Neal). FIFRA in its final form did not incorporate Neal's recommendations.

Though federal officials, consumers, and even manufacturers questioned the efficacy of FIFRA in addressing potential damage to the environment and health, like the Federal Food, Drug, and Cosmetic Act of 1938, FIFRA served as a critical initial step in the development of more comprehensive regulation. Nevertheless, according to environmental scientist John Wargo, the primary risk- management strategy reinforced by FIFRA after World War II was still simply labeling. By requiring labels with instructions for use, the law implied that those who used pesticides could avoid adverse effects by following the directions. Despite the clear notes of concern regarding DDT and other new pesticides sounded during the FIFRA hearings, the law failed to address potential risks to health and the environment. Wargo criticized the legislation as preferential to pesticides manufacturers: "This approach may have done far more to protect the entitlements of the pesticide manufacturers rather than either public health or environmental quality. It sheltered manufacturers from uncoordinated state regulations and may simply have served to provide the public with a false sense of security that pesticide risks were being well contained by USDA. *The reality was that USDA registered pesticides whenever asked*" (Wargo, emphasis added).

## Chemicals in Food Products Hearings: The Delaney Clause and the Miller Amendment

By 1951, concern regarding possible risks associated with insecticides and other chemicals that were finding their way into the food supply inspired a new round of congressional hearings before the House Select Committee to Investigate the Use of Chemicals in Food Products, which took place in the nation's capital and around the country from April 1951 to March 1952. Congressman James J. Delaney of New York chaired the hearings, which became known as the "Chemicals in Food Products" or the "Delaney Hearings." Another key member of the committee was Nebraska Congressman A. I. Miller. Yet it was the committee's chief counsel, Vincent A. Kleinfeld, who examined witnesses utilizing his comprehensive and encyclopedic knowledge of the FFDCA and its amendments as well as the prepared statements and exhibits (Davis).

Over the course of many days of hearings in several venues, including Washington, DC, Washington state, and California, with a transcript of more than 2,700 pages, several critical issues emerged. Congressmen repeatedly returned to their concerns regarding the widespread use of DDT and its potential health effects. Nevertheless, scientific uncertainty permeated the hearings. The views of scientists and public health officials on DDT and other synthetic insecticides ranged widely. Some scientists noted the lack of concrete evidence of harmful effects associated with DDT, and others cited anecdotal evidence of effects from mild to profound in connection with DDT and other chemical insecticides. Yet most participants agreed that the new insecticides had significantly boosted crop yields and contributed to public health since their introduction in the years following World War II. Thus, the Delaney Hearings provide a useful index to congressional interest in pesticides, broad-based uncertainty among scientists, and a sense that such chemicals had quickly emerged as critical to American food production and public health. There was, however, general recognition, particularly among state health officials, that the Insecticide Act of 1910 and the FFDCA of 1938 required revision (Davis).

In the aftermath of the Delaney Hearings, Congress passed two major amendments to the FFDCA. The first was adopted by Congress in 1954 and it became known as the Miller Amendment (§ 408), named for Miller himself. As we have seen, certain legislators and regulators worried that feeding a growing American population required chemical insecticides, while others were concerned about the potential risks that these chemicals, particularly chlorinated hydrocarbons and organophosphates, posed to consumers. The Miller Amendment addressed public health concerns by allowing registration only if manufacturers presented data that demonstrated residue levels on food crops posed no danger to public health. This stipulation granted the FDA the authority to set tolerances for each pesticide and crop, specifically raw agricultural commodities, such as fresh fruits, vegetables, or milk (Wargo).

Yet the amendment limited FDA's regulatory jurisdiction to pesticides used on foods; non-food uses remained under the USDA, even in cases where pesticides could contaminate the environment and eventually produce exposures in foodstuffs. Historian John Perkins argued that the Miller Amendment legitimated the use of insecticides by establishing "insignificant" legal doses (Perkins). According to Bosso, "Congress thus assured the public that, while residues might remain in or on food, the levels were not sufficiently toxic to warrant concern" (Bosso). Under this

amendment, the FDA needed to weigh the benefits of insecticides against the risk. This state of affairs prompted environmental scientist John Wargo to argue, “This dual standard, necessitating the protection of both public and economic health, has become the essence of the nation’s pesticide control strategy, as structured by FIFRA and FFDCA” (Wargo).

In 1958 Congress approved the insertion of the Delaney Clause, which stated: “No additive shall be deemed safe if it is found to induce cancer when ingested by man or animal,” within the general safety clause of the FFDCA (§ 409) (Quoted in Bosso). The Delaney Clause effectively prohibited the FDA, which set food tolerances, from approving any food additive shown to induce cancer in animals or humans. If a food additive (for example, an insecticide) caused cancer, the policy prohibited registration or set the tolerance for approved uses to zero, in effect banning the food additive. The regulatory power of this clause was not lost on legislators who supported the farm bloc: the FDA must ban any suspected carcinogen. Wargo has noted that in passing this legislation, Congress worried that this “zero risk” standard conflicted with the risk- benefit standard that balanced potential risks (toxic residues) with potential benefits (enhanced crop production) (Wargo). According to the environmental historian Nancy Langston, the Delaney Clause had the potential to be revolutionary by stipulating that “any substance known to cause cancer in test animals could not be added to food in any quantity whatsoever” (Langston). Thus, in Langston’s view, the Delaney Clause was a formal, legal expression of precaution, but its focus on carcinogens distracted attention from other hazards.

The first application of the Delaney Clause followed shortly after President Dwight D. Eisenhower signed it into law in November 1958 (Bosso). Barely one year later, HEW Secretary Arthur S. Flemming invoked the clause to advise consumers not to buy cranberries, much to the consternation of growers who objected to the negative publicity so close to Thanksgiving (when 70% of cranberry sales occurred). Flemming noted that some cranberry products on the market had been contaminated with aminotriazole, an herbicide with USDA approval. In 1957 the FDA issued a warning that aminotriazole left unsafe residues on fruit, and it seized and froze contaminated berries for further analysis.

Tests for carcinogenicity took two years and they revealed that aminotriazole caused tumors in rats. These findings precipitated Flemming’s announcement and one of the first cases of something approaching mass hysteria as some states banned cranberries or urged caution. Growers and the USDA attacked Flemming and the FDA, arguing that they had not been consulted nor given adequate notice of the announcement (Bosso).

Desperate countermeasures to reestablish consumer confidence included televised broadcasts of Vice President Nixon and other public figures eating generous portions of cranberry sauce during their Thanksgiving feasts. Despite such efforts, cranberry sales plummeted, and losses to the industry rose to a staggering fifteen to twenty million dollars during 1959 (growers found not to be at fault later recovered ten million dollars in indemnity payments from the USDA). Despite the rather conflicted results of the first application of the Delaney Clause, the hearings and resulting legislation served as a crucial (albeit partial) step in the regulation of chemical pesticides (Bosso).

Congress, in the passage of FIFRA and the prolonged discussions of risks associated with chemical pesticides during the Delaney Hearings, had already begun to evaluate the testimony of

toxicologists both in and out of government. Scientific uncertainty and lack of familiarity with the long-term effects of the newer insecticides stymied legislators' efforts to draw general conclusions regarding risks associated with insecticides. Legislators were asking the questions that needed to be asked, but concrete answers remained elusive as the opinions of experts from the USDA, the FDA, industry, and academia diverged widely. Particularly unclear were the long-term risks associated with DDT and other chlorinated hydrocarbons. Certain target insects developed resistance to DDT, and evidence of transfer from cow to calf prompted USDA advisories regarding the use of DDT in dairy barns as early as 1949. One expert after another acknowledged the dangers of acute poisoning yet wondered about chronic toxicity. Evidence of risk to humans in particular remained murky. Even the nation's leading pro-environmental cancer authority argued that not enough time had passed to determine the tumor-producing potential of DDT in humans. There was no question as to the toxicity and substantial risk of organophosphates, but many believed that their rapid decay offset risks. In striking contrast to most growers and food producers, officials at Beech-Nut Foods adopted a precautionary approach and tested for pesticide residues in its foods.

Despite the uncertainty about pesticides, Congress revised existing legislation to address potential risks. The Miller Amendment restricted residues in foods and empowered the FDA to establish tolerances for foodstuffs. Seeking to minimize the risk of cancer through pesticides, Congress approved the Delaney Clause, stipulating that the FDA set the tolerance for any carcinogenic food additive to zero and effectively prohibiting FDA from registering any food additive shown to be carcinogenic (including pesticides). The first test of the new legislation came when the FDA advised consumers not to purchase cranberries after some cranberry products revealed contamination by aminotriazole. As the market for cranberries collapsed in the midst of mounting consumer panic, the President and Vice President attempted to allay fears and growers defended their product. The cranberry scare brought the problems of chemical food additives and the new legislation to national attention (Davis).

Paraquat was introduced in 1958 in a paper for *Nature*: "A New Herbicide." The authors note that the herbicidal properties of the chemical were discovered in 1955 through research on the herbicidal properties of quaternary ammonium compounds. The authors concluded: "Clearly, 1 : 1'-ethylene-2 : 2' -dipyridylum dibromide is a very potent, translocatable, rapid-acting, non-persistent, post-emergence herbicide... More research is needed before the full potential of this new herbicide can be defined" (Brian et al.).

#### Federal Environmental Pesticide Control Act (FEPCA) - 1972

Amid continuing debates regarding DDT, several prominent court cases regarding pesticides, and nearly two years of hearings focused on deficiencies with FIFRA, Congress passed the Federal Environmental Pesticide Control Act (FEPCA) of 1972. The product of political compromise on the part of the Nixon administration, the bill that led to FEPCA was criticized by both farmers and environmentalists (Flippen). FIFRA required registration once a pesticide was determined to be effective and safe when used as directed. John Wargo noted that FEPCA, in contrast with FIFRA, required manufacturers to "demonstrate that a pesticide would perform its 'intended function' and, 'when used in accordance with widespread and commonly accepted practice,' would not cause 'unreasonable adverse effects on the environment'" (Wargo).

“Unreasonable adverse effects on the environment” applied to both man and the environment and took into account the economic, social, and environmental costs and benefits of the use of any pesticide. Since Congress neglected to define key terms such as “risk,” “cost,” and “benefit,” FEPCA left the EPA in a precarious regulatory position.

The 1972 law did establish two categories for pesticides: general use and restricted use. General use pesticides were unlikely to cause adverse effects; restricted use applied to the more dangerous pesticides that could cause “unreasonable adverse effects” even if used in accordance with label instructions. According to FEPCA, restricted use pesticides could be used only “under direct supervision of a certified applicator.” However, the law allowed for delegation to any competent person under the supervision of a certified applicator. Wargo commented: “The health and safety of the public thus rests on whether the applicator, trained or not, complies with the special precautionary measures provided with the restricted compound” (Wargo). Agricultural chemical manufacturers supported the new legislation because they approved of the certified applicator provision, which was applied to a limited number of chemicals. Designating some pesticides as restricted removed regulatory pressure from the majority of other chemicals. A 1975 amendment further relaxed the restrictions by forbidding the EPA from testing “an applicator’s knowledge of a pesticide’s potential to injure health or the environment” (Wargo).

FIFRA provided the prerogative to suspend or cancel the registration for a pesticide if it posed an “imminent hazard to the public,” without further clarification as to the precise meaning of this phrase. FEPCA, however, defined “imminent hazard” as “a situation which exists when the continued use of a pesticide during the time required for cancellation proceedings would be likely to result in unreasonable adverse effects on the environment or will involve unreasonable hazard to the survival of a species declared endangered by the Secretary of the Interior” (Wargo).

With the passage of FEPCA, it became the EPA’s responsibility to reregister more than fifty thousand chemicals. When the EPA identified that a pesticide had an adverse effect on the environment, it sent cancellation notices to the manufacturers, but such notices merely signaled that the EPA had initiated a review of all available data regarding the chemical’s toxicological and ecological effects. Given the poor quality of data collected by the USDA under FIFRA, such reviews could extend for years, during which time manufacturers continued to produce and distribute the chemical. Moreover, the discovery of the Industrial Bio Test Laboratories scandal and subsequent Congressional hearings further delayed EPA’s review of chemicals for re-registration (see below). One author noted: “Congress plainly did not appreciate the scope of the task it had set before the EPA. It was expected that by October 21, 1976, 50,000 pesticides would be completely re-reviewed. The enormity of this task was compounded in that the EPA had virtually no administrative framework in place” (Gasior). The office of special Pest Reviews (OSPR) was created and charged with the mission of removing from the market pesticides causing unreasonable adverse effects and it was this office that developed the administrative procedure for putting into effect the removal of suspect chemical pesticides: the Rebuttable Presumption Against Registration (RPAR) (Gasior). EPA would later determine that 74% of IBT’s studies were invalid (EPA).

In rare cases when it suspended or canceled a compound, the EPA typically permitted the use of the existing supplies without recall. FIFRA included an indemnification clause that required EPA

“to purchase, collect, and dispose of any recalled products.” Given that most pesticides had been registered by the USDA under the provisions of FIFRA, it proved to be a challenge for the EPA to obtain high- quality evidence regarding toxicity and fate of pesticides for reregistration decisions as well as decisions to classify pesticides for general or restricted use. Most of the data that the USDA collected under FIFRA addressed the efficacy and efficiency of chemicals in controlling pests rather than toxicity and environmental fate. Moreover, much of the data was more than a decade old. Wargo noted, “EPA’s role has therefore been to manage the scientific process, judge the potential for unreasonable hazard, and then adjust existing use entitlements” (Wargo). The challenge of obtaining valid toxicological profiles for pesticides was significantly compounded by problems with the data provided to companies by IBT (see below).

As noted above, FEPCA was supported by industry, especially since one stipulation involved indemnification, the compensation of manufacturers for stocks of pesticides that were either canceled or suspended. Chemical companies viewed indemnification as a form of insurance that was necessary for them to invest in the research and development of new pesticides, a potentially costly enterprise. Some environmentalists came to look upon indemnification as a deterrent to federal suspension or cancellation, since the Office of Pesticide Programs within EPA would bear the costs of indemnification. In fact, as Wargo has shown, between 1972 and 1988, EPA indemnified manufacturers of several herbicides and insecticides, spending in excess of sixty million dollars in the process.

In 1988, Congress revised the indemnification clause and ended financial protection for manufacturers yet continued to protect farmers and applicators who could be indemnified by the regular federal Judgment Fund as directed by the Treasury Department rather than the EPA Office of Pesticide Programs. Despite the challenges posed by classification of pesticides for general or restricted use, re-registration, and indemnification, FEPCA guided pesticide regulation from 1972 forward. Significantly, FEPCA established, as part of federal statute, the protection of the environment as well as human health from the damaging effects of pesticides (Wargo).

EPA Administrator William Ruckelshaus acknowledged that the evidence that DDT was carcinogenic in lab animals did not prove that DDT was threat to humans. Moreover, he believed that “a quick and total ban on DDT would force farmers to resort to highly toxic alternatives.” Nevertheless, in June 1972, after yet another lengthy hearing, Ruckleshaus banned the remaining uses of DDT on crops. He did, however, allow it to be used in cases of urgent public health, such as emergency quarantine. He also allowed for it to be manufactured for export (Davis).

The EPA was called upon to apply FEPCA shortly after it was passed by Congress. The Environmental Defense Fund initiated the legal action in 1968 (i.e., prior to the passage of FEPCA) by petitioning the FDA to reduce to zero all food tolerances for two closely related chlorinated hydrocarbons— aldrin and dieldrin— based on evidence from the Shell Chemical Company study indicating that the compounds caused cancer in mice. The day after EPA opened for business, EDF requested it to suspend and cancel all uses of aldrin and dieldrin. Ruckelshaus, the EPA administrator, complied by issuing a notice of intent to cancel all registrations of the two pesticides. The companies that held the registrations for aldrin and dieldrin demanded review by the National Academy of Science (NAS), which they could do under FIFRA.

After nearly two years, the NAS report reached the conclusion that the pesticides appeared to pose no threat to human health even in their uses as a corn insecticide. EDF next requested that the EPA suspend uses of aldrin and dieldrin through the D.C. Circuit Court in 1972. Cancellation hearings for the two pesticides began in August 1973 after the passage of FEPCA. The new EPA administrator, Russell Train, reviewed testimony generated over the course of twelve months (more than 35,000 pages). Train concluded that aldrin and dieldrin represented an “imminent hazard to man and the environment.” After an expedited suspension hearing, a judge recommended suspension of all uses. Train agreed to the proposal, but Shell Chemical Company appealed, and in April 1975 the D.C. Circuit Court upheld the ruling (Wargo). The cancellation of aldrin and dieldrin took place between 1968 and 1975, which meant that the process began under the rules of FIFRA and concluded under FEPCA.

As with the cancellation of DDT, cancelling aldrin and dieldrin proved to be a labored and tortuous process of requests to FDA then EPA, chemical company appeals, proposed rulings, additional appeals, and, eventually, resolution. As of 1975, the EPA had canceled registrations on several of the persistent chlorinated hydrocarbons that posed the most significant threats to the environment. Meanwhile, many other pesticides remained on the market, including the highly toxic organophosphates. And chemists strove to develop synthetic forms of naturally occurring insecticides.

President Richard M. Nixon established the Environmental Protection Agency in 1970 and transferred principal authority over pesticides from USDA to EPA (Spector 1976). With the passage of FEPCA in 1972, Congress stipulated that “new pesticide products, in order to be registered were to perform their intended function with causing ‘unreasonable adverse effects on the environment’” (Gasior). For much of its early history, EPA was understaffed and underfunded. As a result, the agency’s approach to pesticides has been quite measured. Outright bans on use (or manufacture) are rare. The ban of DDT was the rare exception. It should be noted that Aldrin and Dieldrin were in the same chemical class as DDT (organochlorines or chlorinated hydrocarbons), yet review of these pesticides was a separate and protracted process. Links to industry, including “revolving door” staff who move from agency appointments to corporations have been rife at EPA.

### Federal Pesticide Act of 1978

With the passage of the Federal Pesticide Act of 1978, Congress gave the EPA Administrator the authority to grant conditional registrations for new pesticides as well as to amend currently registered pesticides. Conditional registration effectively allowed pesticide producers to forego full pesticide registration without putting at risk environmental or human health and safety (Lau).

### The Red Book (1982)

In 1982, FDA published *Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food*. In the Preface, the authors noted:

The assurance of safety of all food and color additives is the responsibility of the Food and Drug Administration. Over the last two decades it has become increasingly apparent to those in the government, the public, and the private sectors, that development of information for the assurance of safety can and must be acquired as cost-effectively as possible within the constraints of finite resources. Therefore, it is necessary to provide appropriate guidance regarding the criteria used for food and color additive safety evaluation. Information requirements need to be well defined and commensurate with the potential for the additive to cause safety concerns (FDA).

The “safety” of food and color additives is defined in sections 70.3 and 170.3 of the Code of Federal Regulations (21 CFR 170.3) as a reasonable certainty that a substance is not harmful under the intended conditions of use. The following document represents the latest effort on the part of FDA to delineate the sensitivity and rigor of toxicological and other information needed to make safety determinations for direct food additives and color additives in food. With this document the agency is attempting a better definition of the boundaries of the “reasonable certainty” requirement, while at the same time retaining needed flexibility in this rapidly changing scientific area....

On the whole, the specific requirements of this document do not differ greatly from what the agency now requires for making a safety determination on direct food additives or color additives used in food. What is new is that the basic scheme of scientific decision making for the development of that safety information is now structured around a more cost-effective and flexible framework... (FDA).

Due to its red covers, “Toxicological Principles” became known as the “Red Book” to government and industry toxicologists worked to follow its guidelines for the conduct of studies. The Red Book advised both Acute and Chronic toxicity studies. Acute study included the Acute Oral Toxicity to determine the degree of toxicity of a chemical substance (that is, the relationship between dose and adverse effects), to establish its toxicity relative to other chemical substance whose acute toxicity is known, and to determine specific toxic effects and to provide information on the mode of toxic action. Acute toxicity study would provide information from which the median lethal dose (LD<sub>50</sub>) could be calculated. However, the Red Book noted an important provision: “The numerical value of the median lethal dose (LD<sub>50</sub>) is widely used in toxicity classification systems, but it should not be regarded as an absolute number which identifies the toxicity of a chemical substance. LD<sub>50</sub> values for the same chemical may vary from study to study and between species or within a species because acute toxicity is influenced by both internal and external factors” (FDA).

For Chronic Toxicity Studies, the Red Book emphasized Carcinogenicity Studies and Reproductive Studies. The emphasis on carcinogenicity follows from the Delaney Clause which expressly prohibited additives shown to cause cancer in humans or animals. FDA also proscribed reproductive toxicity studies and studies of teratogenicity (effects of a test substance administered during in utero development).

On neurotoxicity, the Red Book noted: “Compounds which induce neurotoxic signs, symptoms, or effects in any of the required toxicological tests may require special testing. The type of test(s) required will depend upon the review of the data” (FDA).

#### Food Quality Protection Act (1996)

In 1996, President Bill Clinton signed the Food Quality Protection Act (FQPA), which amended both FIFRA (1947) and the FFDCA (1938). FQPA required the EPA to reassess all food tolerances established before August 3, 1996, giving priority to those pesticides posing the greatest risk. This act compelled the EPA to conduct an extensive cumulative risk assessment of the organophosphates. The forty or so organophosphates in use were among the first chemicals the EPA reviewed, followed by the other group of chemicals that induce cholinesterase inhibition: the carbamates. The deadline for the EPA to complete its review of all tolerances was August 2006. Although progress was slow, the EPA announced the phaseout of chlorpyrifos and diazinon based on toxicity and the risk they posed to children through contaminated food and drinking water, as well as their threat to birds and other wildlife (Wargo). At the close of the 2006 cumulative risk assessment, the EPA announced the cancellation of many other pesticides and particularly organophosphates and carbamates. Nevertheless, hundreds of chemical pesticides in thousands of formulations remained on the market.

#### Industrial Bio-Test Laboratories, Chevron Chemical Company, and Paraquat Toxicity Data

IBT was a contract research organization and animal testing facility that conducted studies of Paraquat and other chemicals for Chevron. (Patterson 11-16-20: 115). IBT conducted the chronic toxicity studies that Chevron submitted to the USDA in support of its original Paraquat registration. [Patterson 11-16-20: 24, 100-101; CUSA-00283893] The relationship between IBT and Chevron was riddled with conflicts of interest and lacked objectivity. For example, from at least 1963 through 1975, members of IBT attended meetings with Chevron, ICI, and various regulators to discuss paraquat toxicity and regulatory testing.

SYNG-PQ-02509504; CUSA-00089525; CUSA-00425333; *see also* Patterson 11-16-20: 29-30] IBT also prepared the study protocols, as directed by Chevron, to “soften” Paraquat warning statements. [SYNG-PQ-02509488]

In 1963, ICI scientists noticed “unusually high” mortality rates in IBT’s chronic paraquat study in mice, which ICI was concerned would cause problems with UK authorities. [SYNG-PQ-02509489; SYNG-PQ-02509526] IBT’s founder, Joseph Calandra, assured ICI and Chevron that he would place additional groups of mice in the study to “meet FDA and our requirements.” [SYNG-PQ-0250926] In 1964, Calandra told ICI he was unable to find a correlation between paraquat dose and paraquat residue in the urine of animals used in IBT’s chronic dog study. [SYNG-PQ-02509734] ICI wrote back to Calandra “puzzled” and “disturbed” by his comments, calling it “difficult to understand why dogs on such widely varying paraquat intakes (up to ten-fold) should show no difference in the levels of paraquat excretion.” [SYNG-PQ-02509732; SYNG-PQ-02509727]

In 1964, ICI suggested to Chevron that IBT conduct the subacute inhalation studies for paraquat, advising that the studies could be manipulated to yield any desired result by manipulating the particle size of the aerosol. [SYNG-PQ-02509700] After Chevron submitted IBT's study to the USDA in 1965, ICI realized that IBT's data underestimated the inhalation toxicity of paraquat. [SYNG-PQ-02510034]

In 1966, J.N. Ospenson wrote an internal memorandum revealing that Chevron's paraquat petition contained "a major error and several errors of omission, one of the errors of omission being an exceedingly serious one from the scientific point of view." The serious error was discovered when Chevron saw that IBT's paraquat residue recovery report was identical in every respect to the one submitted a year earlier, and that "no recovery studies had been made whatsoever with this year's test." Ospenson said this omission in some respects "negates the value of the entire project" and that it could render the entire test invalid. Handwriting at the top of this memorandum reveals that the test was ultimately cancelled because IBT could not develop satisfactory recovery data. [CHEV-SJ0125305]

Looking back at IBT's chronic studies in February 1976, Chevron scientists called them "poorly done," and "inadequate for a good defense" of paraquat, noting that one could not even tell what killed the animals in the studies. [Patterson 11-16-20:96-100, 108-110; CUSA-00189780] Also in 1976, ICI's Central Toxicology Laboratory internally reviewed IBT's chronic paraquat study in the rat, calling part of IBT's report "ludicrous" and concluding it would not withstand critical scrutiny. [CUSA-00161987]

However, the problems with IBT's toxicological assessment of Paraquat extended beyond protocols and underestimations. In minutes from a meeting with the Plant Protection Division, Chevron, CTL, and ICI US all present, Cavalli from Chevron reported on the 2-year rat and dog studies conducted at IBT: "Dr. Cavalli told the meeting that IBT had had severe problems at all levels within the organisation apart from right at the top, during the 60's until mid 70's. This had led to a loss in faith in IBT by the FDA/EPA, who are now asking for a complete review of all IBT studies which supported petitions" (ICI / Chevron Liaison Meeting). A Chevron team reviewed a completed IBT study and noted the following:

- no concept of recording of data,
- no dates recorded, only month numbers,
- poor identification of animals,
- one animal died 4 times,
- two-thirds of the experiment were individually housed and one-third 5 per cage - no explanation
- and all data handled in the same manner etc. (ICI / Chevron Liaison Meeting).

In addition, IBT introduced a data destruction program, in theory, after microfilming the data, but the films were not available. Cavalli noted: "As far as Chevron could ascertain, the raw data for both the rat and dog paraquat studies had been destroyed" (ICI / Chevron Liaison Meeting).

Turning to specific studies, there were serious problems with the Mouse carcinogenicity study:

IFHP made the following comments on the previous study:

the tumor data had been handled in an unsophisticated fashion,  
the staff who carried out the study were no longer employed at CTL,

the pathologist at that time did not believe autolysed animals should be examined and consequently there were a large number of animals in the study that were not examined, there were some inconsistencies between the protocol and the study; e.g. 11 animals in some cages; only one group finished with the correct number of animals; other groups fell in the range +/- 2.

In conclusion, considering the number of animals with no histology, the study should not be resurrected. It was accepted that the study should be repeated and the cost was discussed. After further discussion, it was agreed that as much information as possible should be salvaged from the study (i.e., the tissues should be re-read to ensure that tissues not mentioned in the original report were indeed normal)  
(ICI / Chevron Liaison Meeting).

Similar issues were noted with the Reproduction study:

dates of birth missing for some of the early litters,  
no abnormalities,  
changed protocol halfway through study and improved recording system, but no revised protocol,  
stopped measuring food at one stage because 'food unsuitable',  
gross necropsies scheduled to be carried out but no reports available,  
the body weight effect reported was an artefact.

There was consensus that the study should be repeated but delayed to the following March (1978)  
(ICI / Chevron Liaison Meeting).

In addition, the meeting discussed other concerns regarding the RPAR, most notably a draft report of an inhalation study in rabbits (Swan 1969) that claimed rabbits exposed to a paraquat aerosol developed lung changes and urine paraquat level similar to levels in spray workers.

Despite discussions of highly problematic data, the meeting reached a surprisingly positive conclusion: "It is likely that paraquat will be placed in the restricted use category on the basis of prejudices. *Chevron now believe this should not affect sales since air application is already restricted, and it will be relatively easy for most farmers to become certified users.* However, the arguments for putting paraquat in this category are based on dermal and ocular hazards which are not realistic" (ICI / Chevron Liaison Meeting, emphasis added).

In 1976, regulators began investigating IBT after FDA and EPA discovered serious deficiencies in IBT tests conducted to support the registration of numerous drugs and pesticides. [Patterson 11-16-20: 117-18] During that investigation, an FDA scientist discovered that IBT had falsified data for toxicological profiles that companies used to support registration of chemicals. Eventually, the

EPA estimated that IBT generated 35-40% of the toxicological analyses of pesticides in the U.S., including data use for the registration of more than 200 pesticides (Gasior). The re-registration process was suspended in August 1976. It was not re-started until late 1978.

In July 1983, EPA completed its review of IBT: “Thus, the current list of 801 studies covers health effects considered significant to regulatory decisions, such as induction of benign or malignant tumors (oncogenicity), birth defects (teratogenicity), genetic mutations, other adverse reproductive effects, and neurotoxicity. Of the 801 IBT studies in the pivotal categories, 594 (74%) have been found invalid.”

Appendix A: “Chemical Compounds tested by Industrial Bio-test Laboratories” listed Paraquat among the numerous chemicals with IBT listed as presenting the only data on neurotoxicity for the pesticide. Appendix 7: IBT Tracking System Report listed Paraquat and noted that IBT animal studies of inhalation, dermal, oral, and dietary toxicity in a range of animals were almost all invalid (dietary toxicity studies in pheasants were the exceptions).

The IBT scandal significantly delayed the EPA’s re-registration process under FEPCA. The registration process was suspended in August 1976 and it was not restarted until late in 1978. It did not produce results until 1980 (Hoberg). EPA estimated that IBT was responsible for 35-40% of the toxicological tests completed in the U.S. Eventually, EPA determined 74% of IBT’s studies to be invalid (594 out of 801) (EPA, Gasior).

The investigation of IBT led to criminal convictions for falsifying data, and the EPA ultimately determined 15 of the 17 paraquat studies IBT conducted for Chevron were invalid. Patterson 11-16-20: 129-130; Patterson 01-22-21: 59. The studies that replaced the invalid IBT studies were also determined by the EPA to contain “insufficient data” to assess potential chronic health effects from paraquat. ]Patterson 11-16-20:73-75, 129-30]

#### Paraquat not Tested for Neurotoxicity

Before they put paraquat on the market, ICI and Chevron knew that paraquat has a very high potential to participate in redox reactions and produce ROS in the presence of a suitable reductant and oxygen. [2/25/2020 Botham: 70, 79, 86-87; 3/4/2020 Patterson: 152, 166-67; 3/5/2020 Patterson: 270-71. ICI/Syngenta has never conducted a long-term neurotoxicity study of paraquat where an evaluation of cellular loss in the substantia nigra of the test animal was made. [1/5/2021 Botham: 1625-26] In 1965, there was technology available to detect paraquat in the brain tissue of test animals exposed to it. [6/17/2020 Botham: 624] In 1965, the technology was available to analyze brain tissue samples from test animals and persons poisoned by paraquat to see if paraquat was present. [6/25/2020 Patterson 695; see also 6/17/2020 Botham: 624] In 1965, nonhuman primate studies were feasible. [6/17/2020 Botham: 626-27; 6/25/2020 Patterson 697] In 1965, inhalation studies were feasible. [6/25/2020 Patterson: 697] In 1965, lifetime animal tests were feasible. [6/25/2020 Patterson: 697] In 1965, the technology existed to investigate whether exposure to paraquat caused any detectable central nervous system effects. [6/17/2020 Botham: 623] The deficiencies in the studies in Paraquat were known by the companies as Dr. Fletcher of ICI corresponded with Dr. Cavalli stating that the studies that had been done were “old” and

“poorly done. [Deposition of Philip Botham, February 25, 2020, at 198; Deposition of Timothy Patterson, November 16, 2020, at 96 citing Exhibit 84]

Even in the 1960s, 2D and 3D stereology techniques existed that would have allowed researchers to count dopaminergic brain cells in the lab, and nothing prevented Syngenta from buying the necessary equipment and hiring a trained stereologist to do so. [1/16/2021 Botham: 1819] The same is true of Chevron. [1/6/2021 Botham: 1820] So in theory and from a technological standpoint, nothing prevented either company from conducting the same studies that Louise Marks conducted in the early 2000s much earlier. Botham: [1/6/2021 1820-21] Between 1965 and 2003, ICI/Zeneca/Syngenta is not aware of either it or Chevron conducting any neurotoxicity study on paraquat besides a 24-hour rat study conducted by Zeneca in 1995. [6/17/2020 Botham: 529-30]

A long-term, low-dose study in non-human primates could be used to investigate an applicator's exposure to paraquat, but there is no evidence that either ICI or Chevron have done those studies. [1/6/2021 Botham: 193; 6/17/2020: 542-43] Had either ICI or Chevron wanted to perform a study of chronic exposure, either or both of them could have done long-term study in non-human primates to determine the central nervous system effects. [6/17/2020 Botham: 542-43, 558]

#### Failures to Fully Disclose Risks to the EPA

As stated above, it took the manufacturers until 2003 to do long-term neurological animal testing. The testing was completed in response to independent scientists who had done the testing and found neuronal loss in animals. The Syngenta testing confirmed the findings of independent scientists in supporting the neuronal loss. However, the Marks studies were not reported to the EPA for 16 years. [Deposition of Philip Botham, June 17, 2020, at 526]

Further, Syngenta admits to not reporting over 30 studies. [See Exhibit 37, 7/11/2024 Deposition of Monty Dixon] Syngenta chose not to report up to thirty studies that raised serious questions about the safety of paraquat, including the diMonte study, the Mandel/Exponent re-study of the Marks study, and of course, the updated Marks study itself. [Deposition of Philip Botham February 16, 2022, at 407; See also, Deposition of Philip Botham, February 26, 2020, at 363] Additionally, Syngenta failed to report a host of other relevant safety information including communications related to the Brazilian review of Paraquat's neurotoxicity (7/11/2024 Dixon Dep. at 301-306), findings of the absorption of paraquat from the DEFRA study (7/11/2024 Dixon Dep. at 410:6-9), findings of the absorption of paraquat when used in combination with surfactants (7/11/2024 Dixon Dep. 281:6-13), and findings of the ineffectiveness of PPE in stopping Paraquat from being absorbed by users (7/11/2024 Dixon Dep. at 386:22-387:10).

The failures of disclosure related to the safety of Paraquat go beyond neurotoxicity and also involve toxicity related to fatal poisoning. ICI/Syngenta and Chevron's research, however, showed the emetic concentration to not be effective until increased significantly beyond the registration level, evidence that was not shared with the EPA. [See SYNG-PQ-02450673\_R; CUSA-00256363; CUSA-00088442; CUSA-00305732; SYNG-PQ-02451088\_R; SYNG-PQ-02451086] Indeed, the EPA expressed “anguish,” believing that Syngenta “intentionally misused the studies to mislead them. [SYNG-PQ-01655689]

These failures of disclosure of important safety information are both failures under the FIFRA Regulatory scheme (FIFRA Section 6(a)(2)) and the precautionary principles which manufacturers are expected to follow.

### Improper Influence by the Manufacturers on the EPA

The manufacturers of Paraquat wielded significant influence on the EPA and used that influence related to the regulation of Paraquat. The problems with the studies related to IBT are detailed above. The first EPA review of Paraquat following the IBT scandal was subcontracted to a company was subcontracted to a private company Clement Associates. Maurice Green of Clement Associates was an ICI employee a couple of years before he joined Clement Associates. He wrote a letter to ICI telling them about how he received the contract:

"EPA decided to look at all existing pesticide registrations and reconsider the evidence submitted in support of registration in the light of present-day knowledge and of any toxicological data which had been obtained for the compound since registration, and to decide whether to re-register the product, to give a conditional registration and call for more experimental evidence within a set time, or to publish a rebuttable presumption against re-registration of compound. They initially set out to examine all the labels they had approved for various formulations, but this was obviously too large a job. They therefore settled for reconsideration of the active ingredients only and issue of generalized registrations for these. However, this also proved beyond the scope of the present staff, so they handed the whole job over to Clement Associates. We have a \$5 Million contract to develop the risk assessments for 78 existing pesticides. Strangely enough, the first one that EPA sent us was Paraquat. " [SYNG-PQ-13121171]

Upon review of these circumstances, Syngenta admitted that such circumstances would present a conflict of interest under today's standards,

Q. So Maurice Green, the former employee of ICI was going to do the risk benefit analysis on paraquat for the EPA?

A. Yes. And, through today's lens, this all looks a little strange, that you would describe this, perhaps, today as a conflict of interest. But I can assume that, at the time, this was recognized by the EPA to be appropriate.

Further, review of the records reflect not just an appearance of impropriety but impropriety. Documents from Chevron reflected that Clement Associates was "making a poor job" of the reviews undertaken by the EPA and it was agreed that ICI/Chevron would not supply Clement Associates with additional data during the review process. [SYNG-PQ-02515996\_R]

There were and continue to be numerous other instances of influencing the regulatory review. Douglas Wolf served as a health scientist at the US EPA from September 1997 to November 2013 at the Research Triangle Park in North Carolina. He began work at Syngenta in November 2013 (though December 2018) also at Research Triangle Park as well as Greensboro, NC where he was Senior Technical Leader setting strategic goals for regional THS efforts. [Deposition of Douglas Wolf, March 22, 2024; Exhibit 1] Dr. Wolf worked on HESI/RISK21 on behalf of the Environmental Protection Agency, that he expressed interest in and negotiated an agreement to work for Syngenta during that time, and continued to immediately thereafter work on HESI/RISK 21 after he began working at Syngenta because he remained a trustee of HESI/RISK 21's governing organization throughout the entire time. Dr. Wolf admitted that his work on HESI/RISK 21 would be impact Syngenta's ability to maintain registrations such as Paraquat. Id. at 88. Therefore, there was a clear conflict of interest of Dr. Wolf's work at the EPA at the same time he was applying to work for and being hired by Syngenta.

After employment with Syngenta, Dr. Wolf used his background to have Syngenta influence the EPA. Dr. Wolf's knowledge of the key people at EPA who would be most likely to be receptive to proposals from Syngenta was important, and he expressed frustration when some of those key people were not at meetings as he expected. [Deposition of Douglas Wolf, March 22, 2024, at 286-289] Dr. Wolf himself claims credit for being able to leverage his contacts at the EPA on behalf of Syngenta. In his self-description for his nomination to become a Syngenta Fellow, he wrote:

Through my numerous connections with other leaders in risk evaluation and regulatory science and the respect they have for me, I have been able to drive change and push for opportunities to change how chemicals are evaluated for human safety across multiple organizations. I have been applying innovative approaches to inform decision-making and finding opportunities to incorporate new ideas into new AI development projects as well as informing responses to regulatory agencies. These efforts are designed to increase the efficiency of decision-making and decrease the resources necessary to support scientifically defensible risk-based decisions. [SYNG-PQ-12530421]

Other instances of improper influence on the EPA include opposing the EPA Science Panel nomination of Dr. Corey-Slechta, a scientist who conducted multiple studies displaying Paraquat was neurotoxic. [SYNG-PQ-05705351] Syngenta's improper influence on the EPA continues as most recently, Thurston Morton a scientist with the EPA inquired about employment with Syngenta at the same time he was working on the 2019 review of Paraquat. [SYNG-PQ-PA-00033880; SYNG-PQ-08370439]

### Paraquat Widely Banned

It is my belief but for the significant EPA policies in favor of mitigation, the manufacturer's failure to fully disclose relevant safety information, and industry influence, Paraquat would be banned in the United States. In 2022, Pesticides Action Network International published the Consolidated list of Banned Pesticides, which noted that Paraquat had been banned in 58 countries, as of May

2022, including China, where most of the world's Paraquat is currently produced (PAN). Paraquat was banned in the European Union and the United Kingdom in 2007. China banned Paraquat for use in 2016, one year before ChemChina paid \$43 Billion to purchase Syngenta, the manufacturer of Paraquat. EPA re-approved Paraquat in 2023-2024.



Map showing 43 of the more than 70 countries that currently have bans on Paraquat (from Horsfield and Temkin)

#### Conclusion:

The historical and current US Regulatory framework places significant responsibility on the pesticide manufacturers to accurately communicate the risks of their product to the EPA and take appropriate precautionary measures to protect the public. The EPA does not do its own testing. Instead, it relies on information from the manufacturer to accurately report the risks of its pesticides. The EPA further embraces a policy of mitigating those risks and very rarely has banned or rejected registrations of pesticides without the cooperation of the manufacturer.

My historical review of the registration and ongoing EPA approved registration of Paraquat demonstrates the EPA's reliance on information from the manufacturers of Paraquat. Upon review of the deposition testimony and documents related to the regulation of Paraquat, it is my professional opinion that the manufacturers of Paraquat have not behaved responsibly in following the precautionary principle and abused the EPA's reliance on it.

I make these conclusions based on findings outlined in my above report:

A significant body of the studies that established Paraquat's 1965 registration were based on fraudulent data from IBT.

The manufacturers of were aware of serious flaws in the studies conducted by IBT.

The manufacturers were reluctant to alert authorities of the flaws in the data.

The manufacturers were reluctant to conduct studies to replace the IBT studies they knew to be flawed.

The manufacturers refused to conduct neurological testing in light of an awareness of neurological risk.

The manufacturers refused to disclose relevant studies to the EPA.

The manufacturers exerted improper influence on the EPA.

I declare under penalty of perjury that the foregoing statements are true and correct to the best of my knowledge.

Dated: October 04, 2024.

By:



---

Frederick R. Davis

#### References Cited

- Bliss, Chester I. 1935. "The Calculation of the Dose-Mortality Curve." *Annals of Applied Biology* 22: 166.
- Bosso, Christopher. 1987. *Pesticides and Politics: The Life Cycle of a Public Issue*. Pittsburgh: University of Pittsburgh Press.
- Brian, R.C., R.F. Homer, and J. Stubbs. "A New Herbicide: 1 : 1'-ethylene-2 : 2' -dipyridylum dibromide." *Nature* 181 (February 15, 1958): 446-7.
- Corporate documents cited: CHEV-SJ0125305; CUSA-00088442; CUSA-00089525; CUSA-00161987; CUSA-00189780; CUSA-00256363; CUSA-00283893; CUSA-00305732; CUSA-00425333; SYNG-PQ-01655689; SYNG-PQ-02450673\_R; SYNG-PQ-02451086; SYNG-PQ-02451088\_R; SYNG-PQ-02509489; SYNG-PQ-02509504; SYNG-PQ-

02509700; SYNG-PQ-02509727; SYNG-PQ-02509732; SYNG-PQ-02509734; SYNG-PQ-02515996\_R; SYNG-PQ-05705351; SYNG-PQ-08370439; SYNG-PQ-12530421; SYNG-PQ-13121171; SYNG-PQ-PA-00033880

Carpenter, Daniel. 2010. *Reputation and Power: Organization Image and Pharmaceutical Regulation at the FDA*. Princeton: Princeton University Press.

Davis, Frederick Rowe. 2014. *Banned: A History of Pesticides and the Science of Toxicology*. New Haven and London: Yale University Press.

Deposition of Phillip Botham taken 2/25/2020 and exhibits

Deposition of Phillip Botham taken 2/26/2020 and exhibits

Deposition of Phillip Botham taken 3/4/2020 and exhibits

Deposition of Phillip Botham taken 3/5/2020 and exhibits

Deposition of Phillip Botham taken 6/17/2020 and exhibits

Deposition of Phillip Botham taken 2/16/2022 and exhibits

Deposition of Montague Dixon taken 7/11/2024 and exhibits

Deposition of Timothy Patterson taken 6/25/2020 and exhibits

Deposition of Timothy Patterson taken 11/16/2020 and exhibits

Deposition of Timothy Patterson taken 1/5/2021 and exhibits

Deposition of Timothy Patterson taken 1/6/2021 and exhibits

EPA. 1983. "Summary of the IBT Review Program." Office of Pesticide Programs.

FDA Bureau of Foods. 1982. *Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food*.

Flippen, J. Brooks. 1997. "Pests, Pollution, and Politics: The Nixon Administration's Pesticide Policy." *Agricultural History* 71(4): 452.

Gasior, John P. 1989. "Pesticide Safety Regulation Under the Federal Insecticide, Fungicide and Rodenticide Act: Debacle at the EPA." *Fordham Environmental Law Report* 1 (1) 47-68.

Hensill, George S. to Joseph C. Calandra (Letter). 27 Dec 1963. [SYNG-PQ-02509488]

Hoberg, George, Jr. 1990. "Reaganism, Pluralism, and the Politics of Pesticide Regulation." *Policy Sciences* 23(4) (Nov., 1990): 257-289.

Horsfield, Geoff and Alexis Temkin. 2024. "It's Time to Ban Paraquat." Environmental Working Group. URL: <https://www.ewg.org/news-insights/news/2024/02/its-time-ban-paraquat>, Accessed on September 15, 2024.

ICI / Chevron Liaison Meeting (Minutes). 31 Aug 1977. [CUSA-00290556]

Kallet, Arthur and F.J. Schlink. 1933. *100,000,000 Guinea Pigs: Dangers in Everyday Foods, Drugs, and Cosmetics*. New York: Grosset and Dunlap.

Langston, Nancy. 2010. *Toxic Bodies: Hormone Disruptors and the Legacy of DES*, New Haven: Yale University Press.

Lau, Joanna. 2014. "Nothing but Unconditional Love for Conditional Registrations: The Conditional Registration Loophole in the Federal Insecticide, Fungicide, and Rodenticide Act." *Environmental Law* 44(4) (Fall 2014): 1177-1202.

Laug, Edwin P. et al. 1939. "The Toxicology of Some Glycols and Derivatives." *J. Industrial Hygiene and Toxicology* 21 (5): 200.

Neal, P.A. and others, "Toxicity and potential dangers of aerosols, mists, and dusting powders containing DDT," *Public Health Reports*, Supplement No. 177 (1944): 4.

Pesticides Action Network (PAN). 2022. "Consolidated List of Banned Pesticides."

Perkins, John H. 1982. *Insects, Experts, and the Insecticide Crisis: The quest for new management strategies*. New York: Plenum Press.

Sinclair, Upton. 1906. *The Jungle*.

Sobotka, Thomas J. (1992) "Revisions to the FDA's Redbook Guidelines for Toxicity Testing: Neurotoxicity," *Critical Reviews in Food Science and Nutrition* 32(2): 165-171. DOI: 10.1080/10408399209527593

Spector, Phillip L. 1976. "Regulation of Pesticides by the Environmental Protection Agency." *Ecology Law Quarterly* 5 (2) (1976): 233-263.

Swan, A.A.B. to J.C. Calandra (Letter). 21 March 1963. [SYNG-PQ-02509526]

Swan, A.A.B. to R. A. Hamilton (Letter). 11 May 1966. [SYNG-PQ-02510034]

Vos, Bert J. 1980. "History of the U.S. Food and Drug Administration: Retired FDA Pharmacologists." Rockville, MD: National Library of Medicine.

Wargo, John. 1996. *Our Children's Toxic Legacy: How Science and Law Fail to Protect Us from Pesticides*. Yale University Press.

Whitaker, Adelynn Hiller. 1974. "Federal Pesticide Legislation in the United States to 1947." Ph.D. Diss. Emory University.