THE FOOD QUALITY PROTECTION ACT OF 1996: SCIENCE AND LAW AT A CROSSROADS

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"Solely the dose determines that a thing is not a poison.”
- Paracelsus
(1493-1541)**

INTRODUCTION

The Food Quality Protection Act of 1996 ("FQPA")\(^1\) represents a crossroads in both science and law. On the legal side, the FQPA represents a fundamental shift in how we legislate risk regulation. The FQPA takes a step away from bright-line rules strictly delineating standards for risk regulation toward more flexible approaches that acknowledge the need to assess, and where appropriate, implement changing science and technology. On the scientific side, the FQPA represents a basic shift in the end goals of science. In the past, science has sought to discover and understand. Now, the FQPA calls on science to go beyond this traditional goal and synthesize information to allow for the quantification of risks.

The existence of these simultaneous crossroads presents a unique and challenging situation for the regulatory process, which is assigned the task of implementing the fundamental shifts in both science and law. This is a monumental challenge for a regulatory state that is already receiving harsh criticism for its current shortcomings. This article defines the crossroads in science and law and then discusses how the regulatory process might successfully handle the new challenges it faces.

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** CASARETT & DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS i (Curtis D. Klaassen et al. eds., 5th ed. 1996).

The first part of this article will explore the crossroads in law created by the restructuring of the Delaney Clause in the Food Quality Protection Act of 1996. The Delaney Clause, found in the Federal Food, Drug, and Cosmetic Act ("FFDCA"), places a simple, strict ban on carcinogenic food additives. First, the history of the Delaney Clause and its relation to regulation of pesticide residues in our food supply will be discussed. Second, the problems and criticisms that have arisen over the Delaney Clause will be highlighted. Third, the changes in the FFDCA brought about by the FQPA's fundamental shift to a more flexible legislative approach to risk regulation will be delineated with special emphasis on restructuring of the Delaney Clause. Finally, the case of a regulated pesticide, the fungicide benomyl, will be discussed to demonstrate how the FQPA will affect pesticide regulation.

The second part of this article will discuss the crossroads in science by using chemical carcinogenesis and cancer risk assessment, both at the heart of Delaney Clause regulation, as illustrative examples. First, the crossroads in science is defined as a fundamental expansion of the traditional goals of discovery and understanding to include the more synthetic goals of processing information to produce quantified risk estimates. Second, the pathology of chemical carcinogenesis will be outlined with an emphasis on its complex and dynamic nature. Third, cancer risk assessment will be discussed to illustrate how science is facing the expansion of its traditional goals. The current and future trends in cancer risk assessment will be highlighted to demonstrate science's movement toward more flexible approaches, a shift that is not unlike the shift occurring in law. Finally, an analogy will be drawn between chemical carcinogenesis and developmental toxicity to show that similar changes are occurring in many areas of regulatory toxicology.

The third part of this article explores the challenges for the regulatory state that result from the crossroads in science and law. The FQPA places a wealth of new and dynamic information at the door of the regulatory process and depends on the regulatory process to effectively handle this burden. Successful regulation will depend on effective regulatory analysis and better risk communication to aid the analysis. Effective analysis will be discussed with emphasis on what traits the regulatory process will need to accomplish this goal. Then, the problem of communicating to the public those decisions made at the analysis stage will be briefly explored. Suggestions for
improving the communication stage will be presented, with a focus on developing trust and credibility in the regulatory process.

Finally, the importance of recognition by the regulatory process of the crossroads in science and law will be emphasized. The Environmental Protection Agency ("EPA") has a critical role in this recognition stage. Successfully acknowledging its position and accommodating its new role will be imperative in establishing and maintaining a successful EPA and regulatory process.

I. THE FOOD QUALITY PROTECTION ACT OF 1996: LAW AT A CROSSROADS.

During the 1950's, New York Representative James J. Delaney chaired a House Select Committee to investigate the use of chemicals in food products. Convinced that too many chemicals were being introduced into the nation's food supply, Delaney voiced his opinion in response to the Food and Drug Administration's ("FDA") approval of a known carcinogen, the pesticide Aramite, for use as a food additive:

The part that chemical additives play in the cancer picture may not yet be completely understood, but enough is known to put us on our guard. The safety of the public health demands that chemical additives should be specifically pretested for carcinogenicity, and this should be spelled out in the law. The precedent established by the Aramite decision has opened the door, even if only a little, to the use of carcinogens in our foods. That door should be slammed shut and locked. That is the purpose of my anticarcinogen provision.

Witnesses who testified before Congress during the 1950's stressed that current scientific techniques could not determine a safe level for carcinogens and, therefore, all carcinogens should be banned from the


food supply.\textsuperscript{4} Congressional concern culminated in the incorporation of the "Delaney Clause" into the Food Additives Amendment of 1958. The Delaney Clause is codified in sections 409(c)(3)(A), 706(b)(5)(B), and 512(d)(1)(H) of the FFDCA. Section 409 states "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal . . . .\textsuperscript{5}" Enactment of the Delaney Clause in section 409 of the FFDCA established a zero-risk policy for carcinogenic food additives. Courts in subsequent years repeatedly interpreted the clause to be an absolute bar to all such additives regardless of the actual risk involved.\textsuperscript{6}

The Delaney Clause represents a relic of the scientific past. At the time of Congressman Delaney, science lacked the tools to properly cope with problems such as cancer, making strict, bright-line legislation such as the Delaney Clause necessary. As our knowledge of cancer has evolved, it has become apparent that adherence to a zero-risk standard is impractical, if not impossible. Technological achievement has eroded the foundations of legislation such as the Delaney Clause, creating widespread criticism and need for reform of such laws.

On August 3, 1996, President Clinton signed the FQPA, ushering in a new era for agricultural and food industries. The FQPA greatly modifies existing portions of the FFDCA and signifies an important step away from the Delaney Clause's strict ban on using carcinogenic substances as food additives. The FQPA does not eliminate the Delaney Clause, but does markedly limit its jurisdictional scope.

A. The Delaney Clause and Pesticides

One of the original purposes of the Delaney Clause was to protect our food supply from unwanted pesticide contamination. Congress divided this burden between two Acts to be administered by several different agencies. Registration for the production and use of


\textsuperscript{6} See \emph{Les}, 968 F.2d at 989-90; Public Citizen v. Young, 831 F.2d 1108, 1112 (D.C. Cir. 1987).
pesticides is regulated by the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"). Pesticide residues in our food supply are regulated by the FFDCA. EPA is responsible for setting tolerances (the maximum allowable safe levels of a substance in or on a food) for pesticide residues; the FDA and the U.S. Department of Agriculture ("USDA") are responsible for enforcing the tolerances.

Three sections of the FFDCA guide the regulation of pesticide residues in our food. Section 402 defines foods that are adulterated, or unusable, and consequently banned from consumer markets. Section 408 guides the determination of unsafe pesticide residues on raw foods, while section 409 applies to unsafe food additives. These sections provide the framework for setting tolerances to delineate safe levels of substances in or on foods. Exemptions from tolerances may be granted when the tolerance is "not necessary to protect the public health."
If an exemption is not granted, and the food fails to meet tolerance requirements, it is deemed adulterated under section 402. Problems arise because the FFDCA classifies pesticide residues on raw and processed foods differently. Under section 402(a)(2), if a pesticide residue on a raw food concentrates during processing, meaning that the residue on the processed food is greater than the residue on the raw food, the residue on the processed food is considered a food additive and is regulated under section 409. Otherwise, pesticide residues on or in processed foods are regulated under section 408. Section 408 contains a flow-through provision allowing tolerances for residues on raw foods to flow through to processed foods. Thus, tolerances for raw foods and uncleared residues in processed foods are set under section 408, dealing specifically with pesticides, while tolerances for residues which are known to concentrate in processed foods are set under section 409, dealing with food additives in general. The important distinction between the two statutory sections is the presence of the Delaney Clause in only section 409.

Section 408 allows tolerances for pesticides to be set based on a risk-benefit analysis, while section 409 adheres to the Delaney Clause's zero-risk standard. EPA has maintained a strict interpretation of the Delaney Clause in section 409 and, consequently, if any portion of a crop to which a carcinogenic pesticide has been applied is processed in a way that will cause concentration of the pesticide residue, EPA's policy has been to deny section 409 clearance for the processed food as well as denying a section 408 tolerance for the raw food. When required section 408 tolerances cannot be granted, EPA is also required to deny registration of the pesticide under FIFRA. This differential treatment of raw and processed foods has become known as the "Delaney Paradox" and has caused the

13. The FFDCA § 408 allows tolerances for pesticides in or on raw agricultural commodities to be set with consideration given to "the necessity for the production of an adequate, wholesome, and economical food supply ...." 21 U.S.C. § 346a(b) (1994).
15. Id.
registration of many pesticides to hinge on whether they concentrate in food processing.

B. Criticism of the Delaney Clause

The Delaney Clause has been criticized repeatedly because it is responsible for major pitfalls in new product development and creates recurring problems with products already on the market. The Delaney Clause also creates an unnecessary fear of some cancer risks, dividing limited resources disproportionately between cancer risk assessment and other types of risk assessment.

According to a 1987 National Research Council survey of Research and Development directors of twenty major pesticide manufacturers, new product development is significantly hindered by the Delaney Clause. Respondents estimated that research and development (R&D) costs for a new product eliciting an undisputed carcinogenic response and having use patterns in processed foods which require a section 409 clearance would be reduced by an average of five to fifteen percent if the Delaney Clause did not apply and the risk-benefit analysis of section 408 governed registration.16 Almost unanimously, respondents agreed that chances of actually receiving section 409 clearance for such a product under the Delaney Clause would be practically nonexistent, while under risk-benefit analysis chances would be around fifty percent.17 Additionally, respondents felt that research and development time could be reduced by one to two years if the Delaney Clause were eliminated.18

More imminent problems created by the Delaney Clause lie in reregistration of older pesticides. FIFRA requires reregistration of any pesticide registered before November 1, 1984.19 Reregistration poses many potential problems for pesticide manufacturers because EPA has instituted programs to greatly expand its toxicological data on pesticides.20 Older pesticides tested under new EPA standards are far more likely to be identified as carcinogenic as well as more

16. Id. at 249. To clarify, the 5-15 percent reduction in R&D costs represents the costs of performing the additional section 409 tests for carcinogenicity that would be required to seek a tolerance under that section.

17. Id. at 250.

18. Id.


likely to be found to concentrate in processed foods. The combination of these factors would force EPA to ban many older pesticides under the Delaney Clause regardless of other factors, such as lack of replacement pesticides or the need of a pesticide to prevent epidemic disease.

The problems created by the Delaney Clause reach beyond the pesticide industry. The application of the Delaney Clause may limit the introduction of newer, less toxic pesticides to replace older, more dangerous ones. Other critics argue the Delaney Clause forces research and development programs to divert funds disproportionately to cancer studies. They argue that the Delaney Clause has singled out one health endpoint, cancer, and has overlooked other more pressing health issues such as neurotoxicity, developmental toxicity, endocrine disruption, and immunological disorders. Additionally, Bruce Ames, a researcher at the University of California-Berkley, argues that 99.99 percent of pesticides we ingest occur naturally in plants so reducing our exposure to the other 0.01 percent that are synthetic will have no effect on cancer rates. He proposes that modern risk assessment methods are flawed in that linear extrapolation from near-toxic doses in rodents to low-level exposures in humans has led to grossly exaggerated cancer risks and an imbalance in society’s perception of hazard and the allocation of resources. Further, modern analytical techniques allow for the detection of pesticide residues at levels up to one million times lower than possible 30 years ago at the inception of the Delaney Clause. Ames concludes that regulating trivial risks, as the Delaney Clause often requires, impedes effective risk management and may divert resources from much more important health risks that urgently need to be addressed.

Criticisms of the Delaney Clause led to a National Research Council study on the regulation of pesticides. The 1987 study concluded that progress toward uniform risk reduction would be greatest and most uniform when raw and processed foods were

21. Id.
22. See Vogt, supra note 2, at 3.
23. Id.
26. Id.
27. Id. at 63; see also Breyer, supra note 24, at 3-29.
subjected to the same standard. The study suggested using a negligible risk standard with no consideration of benefits. The study defined negligible risk to be the level at which cancer risks from a pesticide residue do not exceed one in one million (1x10^-6) over a 70-year lifetime. In the 1992 case Les v. Reilly, the Ninth Circuit acknowledged the need for change from the outdated Delaney Clause standard, and called upon Congress to reform the statute. On February 27, 1996, Michael W. Pariza, Director of the Food Research Institute at the University of Wisconsin-Madison, testified before the Subcommittee on Health and Environment of the House Committee on Commerce, stating that:

One of the most urgent matters bearing on competitiveness and innovation in the nation’s food industry is comprehensive Delaney reform. No doubt the Delaney Clause seemed like a good idea in 1958, but we know today that this legislation is seriously disconnected from scientific reality... No other nation on earth has burdened its regulatory authorities and food industries with a policy like Delaney. This outmoded legislation wastes resources, mis-directs public concern away from important issues, has a stifling effect on innovation, and impedes competitiveness. It is imperative that Delaney be replaced with a flexible science-based policy ...

Criticism of the Delaney Clause finally culminated in 1996 with the signing of the FQPA.

28. REGULATING PESTICIDES, supra note 14, at 7. The study examined four possible scenarios. The first was applying zero-risk to raw and processed foods; the second was applying zero-risk to all pesticide residues in processed foods (this method assumed that if a residue was detected in a processed food, tolerances for both the processed and raw foods would be revoked); third was to revoke all tolerances when combined estimated cancer risk from the residues of the pesticide on raw and processed foods exceeds 1 in 1 million over a 70-year lifetime; and fourth was to revoke all tolerances when the total risk from residues of the pesticide on all processed forms of a crop exceeds 1 in 1 million over a 70-year lifetime (this method assumed that if a residue exceeded the prescribed tolerance in a processed food, tolerances for both the processed and raw foods would be revoked). Id. at 6.

29. Id. at 39. This is the established level at which the FDA has determined the assessed risk from cancer to be insignificant. Id.


31. The Need for FDA Reform of Food Regulation: Hearing on The Need for FDA Reform Before the Subcomm. on Health and Env’t of the House Comm. on Commerce, 104th Cong., 2d Sess. 2 (1996).
C. The Food Quality Protection Act of 1996

The FQPA is an extensive piece of legislation that deals with far more than just Delaney Clause reform. However, Delaney Clause reform is a prominent feature of the legislation. The FQPA addresses the Delaney Clause specifically in regard to pesticide residues. The law does not eliminate the Delaney Clause, as it still remains in effect for food additives other than pesticide residues. The FQPA is intended to establish a more uniform regulatory scheme for pesticides that is grounded in modern toxicological science and that balances risks with the social and economic well-being of our nation.  

The FQPA amends several definitions to the FFDCA. The FQPA redefines the exceptions to the definition of “food additive” to exempt “a pesticide chemical residue in or on a raw agricultural commodity or processed food; or (2) a pesticide chemical . . . .”  

“Pesticide chemical residue” is now clearly defined as “a residue in or on a raw agricultural commodity or processed food of— (A) a pesticide chemical; or (B) any other added substance that is present on or in the commodity or food primarily as a result of the metabolism or degradation of a pesticide chemical.”  

“Processed food” is defined as “any food other than a raw agricultural commodity and includes any raw agricultural commodity that has been subject to processing, such as canning, cooking, freezing, dehydration, or milling.”  

These changes alter the old FFDCA exceptions to food additive status to allow pesticide residues on raw and processed foods to be treated equally.  

Section 404 of the FQPA amends section 402 of the FFDCA to state the following:  

A food shall be deemed to be adulterated - (2)(A) if it bears or contains any added poisonous or added deleterious

34. § 402(a), 110 Stat. at 1513. Metabolic products of the pesticide are clearly addressed in the new definition. This is significant because it reflects modern science’s increased understanding of toxicology and the effects of xenobiotic compounds. It allows EPA to regulate substances that may not be toxic in their bioavailable form but do become toxic as a natural consequence of the body’s attempt to metabolize them.  
35. § 402(c), 110 Stat. at 1513-14.  
substance (other than a substance that is a pesticide chemical residue in or on a raw agricultural commodity or processed food, a food additive, a color additive, or a new animal drug) that is unsafe within the meaning of section 406; or (B) if it bears or contains a pesticide chemical residue that is unsafe within the meaning of section 408(a); or (C) if it is or if it bears or contains (I) any food additive that is unsafe within the meaning of section 409...

The new definition clearly distinguishes between pesticide residues in processed foods and food additives. Under the new scheme, pesticide residues on or in processed foods will be regulated with pesticide residues on raw foods under section 408, regardless of whether the residues concentrate during processing, while substances remaining within the FQPA’s amended definition of food additives will be subject to section 409 regulations and the Delaney Clause. EPA is now allowed to set tolerances for all residues of registered pesticides based on a risk-benefit analysis.

In addition to making a clear and uniform distinction between pesticide residues and food additives, the new statute grants EPA significant flexibility in regulating pesticide residues and setting tolerances. The FQPA rewrites most of section 408 of the FFDCA. The flow-through provision, removed from section 402, is re-inserted into section 408(a)(2). Section 408(b) continues to allow EPA to use a risk-benefit analysis when setting tolerances and requires that certain criteria be factored into the analysis. Section 408(b)(2)(B)(v) directs EPA to review tolerances every five years to allow new scientific evidence to be assessed where it is applicable. Finally, the new section 408(b) specifically requires EPA to evaluate

41. Id. at 1515-20.
42. Id. at 1517.
data on the effects of pesticides on infants and children\textsuperscript{43} and to evaluate whether certain substances may have effects on humans similar to the effects produced by naturally occurring estrogen or other hormones.\textsuperscript{44}

Section 408(b)(2)(A)(ii) defines "safe" for the purpose of setting tolerances as "a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."\textsuperscript{45} In making a determination of safety, the FQPA allows EPA to consider such factors as the validity of scientific data, anticipated and actual residues of the pesticide in or on foods, the percent of food actually treated with the pesticide,\textsuperscript{46} and international standards.\textsuperscript{47} This new framework establishes a "reasonable certainty of no harm" standard for determining safe levels of pesticide residues in food.

Notably absent from the final version of the FQPA is an additional subsection that would have prevented assessment of economic effects on the registrant, manufacturer, or marketer of the pesticide when setting tolerances.\textsuperscript{48} This makes it likely that such factors will be considered by EPA in the future. The FQPA also adds a consumer information clause\textsuperscript{49} and a provision which prevents individual states from setting pesticide residue tolerance levels higher


\textsuperscript{44} § 408(p), 110 Stat. at 1532-33. EPA must develop a screening program for estrogen-mimicking pesticide chemicals that will test all current and future use pesticides. \textit{Id.}

\textsuperscript{45} § 408(b)(2)(A)(ii), 110 Stat. at 1516.

\textsuperscript{46} § 408(b)(2)(D)-(F), 110 Stat. at 1518-19.

\textsuperscript{47} § 408(b)(4), 110 Stat. at 1520. EPA must consider established International Codex Alimentarius Commission maximum residue levels for the pesticide. If EPA decides to set a different level, EPA must publish for public comments its reasons for the different level. \textit{Id.}


\textsuperscript{49} § 408(o), 100 Stat. at 1532. EPA must provide information that discusses risks and benefits of pesticide use on foods, explains tolerances, and provides recommendations for ways to reduce dietary exposure to pesticide residues for public display by large retail grocers. \textit{Id.}
than those established nationally. Finally, the FQPA mandates that EPA must, within 10 years, review all pesticide tolerances in effect as of the signing of the FQPA.

In sum, the FQPA makes significant changes to the FFDCA that will allow EPA to treat pesticide residues on raw and processed foods uniformly regardless of effects of processing on residue concentrations. The revisions to section 408 provide EPA with more flexibility for performing risk analysis, by allowing EPA to consider more risk factors in setting tolerances. Simultaneously EPA is given more power to consider the benefits of pesticide use. Section 409, containing the Delaney Clause, is left intact, thus, maintaining a zero-risk policy for carcinogenic food additives other than pesticide residues.

D. The Case of Benomyl

The FQPA will have a significant impact on pesticide production and use in general, and on future regulation of fungicides in particular. The estimated dietary carcinogenic risk associated with fungicides represents approximately 85 percent of all dietary carcinogenic risk from pesticides. As many of the fungicides in widespread use have come up for reregistration, new scientific data has proven them to be carcinogenic. The FQPA will allow a much more fair and uniform assessment of these pesticides. The case of the fungicide benomyl illustrates this well.

Benomyl (methyl 1-[(butylamino) carbonyl]-H-benzimidazol-2-yl carbamate) is a systemic, benzimidazole fungicide that is used against a wide range of fungal diseases of field crops, fruits, nuts, ornamentals, mushrooms, and turfgrass. It has a relatively short half-life in the environment — three to six months when applied to turf and six to twelve months when applied to bare soil. In the human body, it is rapidly broken down to carbendazim and then to other compounds before being excreted. Benomyl and its metabolites have not

50. § 408(n), 110 Stat. at 1530-32. A state may petition EPA for authorization to set a level higher than the national level and EPA may grant such authorizations at its discretion. § 408(n)(5), 110 Stat. at 1531.
51. § 408(q), 110 Stat. at 1534-35.
52. See REGULATING PESTICIDES, supra note 14, at 97.
54. Id. at 3.
been found to bioaccumulate in human fat and muscle tissues over long term exposure periods.\textsuperscript{55}

Benomyl is classified by the World Health Organization as a class III+ pesticide, the World Health Organization’s safest classification for pesticides, meaning the pesticide is unlikely to present hazard under normal use.\textsuperscript{56} The Reference Dose ("RfD") of benomyl is 0.05 mg/kg/day and the Acceptable Daily Intake ("ADI") is 0.02 mg/Kg/day.\textsuperscript{57} Benomyl is of such a low acute toxicity that it has been impossible to establish an LD\textsubscript{50} for mammals.\textsuperscript{58} The LD\textsubscript{50} for rats is greater than 10,000 mg/Kg and for rabbits is greater than 3400 mg/Kg.\textsuperscript{59}

Benomyl has shown chronic toxicity in the form of severe liver impairment in dogs fed doses of 150 mg/Kg/day in their diets for two years.\textsuperscript{60} The pesticide caused no reproductive effects in a three-generation study of rats fed low doses (150 mg/Kg/day), while at higher doses, viability and fertility of offspring was decreased.\textsuperscript{61} Teratogenicity (fetal toxicity) has been observed in rats and mice at

\textsuperscript{55} Id.
\textsuperscript{56} Donald J. Ecobichon, Toxic Effects of Pesticides, in CASARETT & DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS 682 (Curtis D. Klaassen et al. eds., 5th ed. 1996).
\textsuperscript{57} Benomyl, supra note 53, at 4. The RfD is an estimate of the daily exposure to an agent that is assumed to be without an adverse health impact on the human population. The ADI is used by the World Health Organization for pesticides and food additives to define "the daily intake of chemical, which during an entire lifetime appears to be without appreciable risk on the basis of all known facts at that time." Elaine M. Faustman & Gilbert S. Omenn, Risk Assessment, in CASARETT AND DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS, supra note 57, at 80 (citing World Health Organization, Principles Governing Consumer Safety in Relation to Pesticide Residues, WHO TECH. REP. SER. 240 (1962)). Both are calculated as follows:

\[(RfD) \text{ or } (ADI) = \text{NOAEL/UF}\text{*MF}\]

where NOAEL = No Observed Adverse Effects Level as determined by animal bioassays; UF = Uncertainty Factors and MF = Modifying factors used to account for variations caused by extrapolations from test models. Elaine M. Faustman & Gilbert S. Omenn, Risk Assessment, in CASARETT AND DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS, supra note 56, at 80-81.

\textsuperscript{58} Benomyl, supra note 53, at 1. The LD\textsubscript{50} is the median lethal dose, or the statistically derived single dose of a substance expected to cause death in 50 percent of the animals tested. David L. Eaton & Curtis D. Klaassen, Principles of Toxicology, in CASARETT & DOULL'S TOXICOLOGY: THE BASIC SCIENCE OF POISONS, supra note 56, at 21.

\textsuperscript{59} Benomyl, supra note 53, at 1.
\textsuperscript{60} Id. at 2.
\textsuperscript{61} Id.
doses of 62.5 mg/Kg and 100 mg/Kg respectively. However, no teratogenicity has been observed in human studies. Carcinogenic effects on liver cells have been observed in mice in lifetime studies at doses of about 40 to 400 mg/Kg/day with the metabolite carbendazim being the likely ultimate carcinogen. Because of conflicting data, EPA has classified benomyl as only a possible human carcinogen. Benomyl was first registered by DuPont in 1972 and by 1987 it accounted for approximately 55 percent of the $320 million worldwide benzimidazole fungicide market. A special review of benomyl was initiated in the late 1970's, and, as a result of that review, its possible carcinogenicity was discovered.

EPA announced its findings regarding benomyl's cancer risk in October 1988 and refused to revoke existing tolerances for use on tomato products and raisins, both foods in which residues of benomyl are known to concentrate during processing. EPA simultaneously announced a new interpretation of the Delaney Clause permitting concentrated carcinogenic pesticide residues in processed foods as long as they posed only a de minimis risk of cancer, set at one in one million (1x10^-6) over a 70-year lifetime. In essence, EPA acknowledged the obligation to revoke tolerances for tomato products and raisins, but refused to do so. EPA's new interpretation was rejected by the Ninth Circuit in Les v. Reilly. EPA was instructed to strictly interpret the Delaney Clause and revoke the tolerances at issue. As a result of the court's decision, EPA revoked tolerances in 1993 and issued a final rule for decision in 1994.

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62. CATALOG OF TERATOGENIC AGENTS 244 (Thomas H. Shephard ed., 8th ed. 1995). Typical teratogenic effects observed in rats and mice were hydrocephalus, cleft palates, hydronephrosis, and skeletal defects. A human study of 900,000 people found no teratogenic association between benomyl and eye defects. Id.
63. Id.
64. Benomyl, supra note 53, at 2.
65. Id.
66. REGULATING PESTICIDES, supra note 14, at 198.
67. 40 C.F.R. § 185.350 (1995). The tolerance level is set at 50 ppm (mg/Kg) for both foods. Id.
69. See Les v. Reilly, 968 F.2d 985 (9th Cir. 1992).
es was never implemented and, following passage of the FQPA, the final revocation actions were withdrawn by EPA in September 1996.\textsuperscript{72}

The FQPA will have a profound impact on benomyl. Benomyl is now excepted from the definition of food additive, and thus tolerances for tomato products and raisins will no longer fall under the purview of section 409 of the FFDCA. Consequently, benomyl residues are no longer subject to the Delaney Clause. Those tolerances will now be set using the risk-benefit analysis of section 408. Under section 408, a "reasonable certainty of no harm" standard will provide a more flexible framework for the setting of a safe tolerance. Under this framework, EPA is likely to approve the use of benomyl on tomatoes and raisins, as evidenced by their 1988 decision to list the pesticide as posing a \textit{de minimis} risk of causing cancer.\textsuperscript{73}

EPA possesses extensive data on benomyl and will be capable of making an informed decision before approving a tolerance. Section 408 now gives EPA more flexibility in considering factors when assessing benomyl's health risks. EPA will now evaluate the developmental, endocrinical and carcinogenic effects of benomyl and its metabolites using modern risk assessment techniques. In addition, EPA may now also assess such factors as benomyl's widespread use and the multimillion dollar costs farmers will face if forced to substitute other pesticides.\textsuperscript{74}

The approval of benomyl may or may not be a good decision. On one hand, the compound has an extremely low acute toxicity, is not persistent in the environment or the human body, and poses a questionable, but likely inconsequential, risk of cancer. On the other hand, benomyl's widespread use makes the compound highly bioavailable for human consumption, and the compound has been found to cause definite teratogenic effects in animal studies. The FQPA mandates that some of these issues, such as teratogenicity, be explored more fully in setting pesticide residue tolerance levels. The FQPA will enable EPA to fully benomyl and its uses fully and will lead to a decision on tolerances that is scientifically, economically, and socially more sound than the outdated strict application of the Delaney Clause.

\textsuperscript{74} See 58 Fed. Reg. at 37,865.
The FQPA represents a turning point in the law. Tracing the events that have led to passage of the FQPA demonstrates how the law is recognizing the need for a flexible approach to risk regulation that frees regulatory agencies to adapt and implement new scientific discoveries and techniques as they become available. Institution of this flexible approach places science at a crossroads as well. Science is now faced with the responsibility of improving existing knowledge and techniques to provide the regulatory process with effective tools to carry out risk regulation.

II. SCIENCE AT THE CROSSROADS

The FQPA significantly expands the use of risk-benefit analysis in risk regulation and relies on science to provide the knowledge and tools necessary to quantify risks and build a foundation for effective regulation. This signifies a fundamental shift in science. Science in the past has sought to discover and understand. Now, science must extend beyond discovery and understanding to synthesize information and quantify risks. Science faces this crossroads in all aspects of risk regulation. With the FQPA, Congress has acknowledged that science is now capable of and responsible for providing risk estimations that better serve society.75

Perhaps the most illustrative example of the scientific crossroads is chemical carcinogenesis. During the time of Congressman Delaney, cancer development was poorly understood. However, the past forty years have seen remarkable advances in science's understanding of cancer development. Chemical carcinogenesis research has uncovered a type of environmental risk that is tremendously dynamic and diverse. Researchers have discovered that chemical carcinogenesis is a multi-stage disease that can occur through a number of different pathways. Simultaneously, risk assessment is rapidly developing methods to deal with these discoveries and produce more accurate models of risk. Exploring the current body of scientific information

about chemical carcinogenesis and cancer risk assessment illustrates science’s new position in our society.

A. Chemical carcinogenesis

Cancer is a broad term describing a subset of lesions of the disease neoplasia, an abnormal autonomous growth of tissue.\(^7\) Such tissues, referred to as neoplasms or, more commonly, tumors, may be benign or malignant, the latter being differentiated by uncontrolled secondary growth.\(^7\) Carcinogenesis is the transformation of normal tissue to a neoplasm, and a carcinogen is an agent that causes or induces this transformation.\(^7\) Established carcinogens include many environmental chemicals such as benzo[a]pyrene (a primary component of cigarette smoke), benzene, polycyclic aromatic hydrocarbons, and many pesticides.\(^7\)

Alteration of DNA structure at the molecular level is the underlying cause of carcinogenesis.\(^8\) Physically or chemically altered DNA structures are termed adducts or lesions. Adduct formation is a common occurrence in normal cellular functioning and does not necessarily equate to cancer.\(^8\) Cellular systems have evolved several mechanisms to protect against DNA adducts, such as direct DNA repair and programmed apoptosis (cell death), both acting to prevent replication and growth of mutated cells.\(^8\)

At least four major mechanisms of chemical carcinogenesis have been identified. They include electrophilic interactions, oxidative

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77. *Id.*
78. *Id.* at 202. Carcinogenesis includes the induction of neoplasms that are usually not observed, the earlier induction of neoplasms that are usually observed, and the increased induction of neoplasms. *Id.* In essence, carcinogenesis is a term used to describe a series of events resulting in a described outcome. The order and nature of the events can be greatly varied and can occur spontaneously or as a result of either direct or indirect contact with a stimuli.
79. *Id.* at 245.
80. *Id.* at 214-26.
81. *Id.*
82. *Id.* at 225-35. Direct repair of DNA may occur via enzymatic reactions involving direct reversal of DNA damage, base excision repair, nucleotide excision repair, postreplication repair, and mismatch repair. The persistence of DNA adducts results from the failure of endogenous repair systems and is directly correlated to incidences of neoplasia. The ability to endogenously cope with DNA damage is strongly influenced by genetic factors and varies greatly from one individual to the next. *Id.* at 221-26.
DNA damage, increased development of background tumors, and receptor protein interactions. Each mechanism is complex and may occur naturally or as a result of exposure to chemical agents. These mechanisms may or may not lead to advanced stages of cancer development and may act independently or in conjunction with other mechanisms.

Alteration of DNA at the molecular level may occur rapidly, but the development of cancer as a disease is a slow process involving a long latency period characterized by three stages between first exposure to a chemical carcinogen and an ultimate malignant neoplasm. The first stage is initiation, in which an irreversible change occurs in the DNA of a single cell. Initiation may occur rapidly, but the development of cancer as a disease is a slow process involving a long latency period characterized by three stages between first exposure to a chemical carcinogen and an ultimate malignant neoplasm. The first stage is initiation, in which an irreversible change occurs in the DNA of a single cell. Initiation may occur spontaneously as a result of natural processes or the introduction of exogenous chemical compounds. Id. Adducts formed by electrophilic interactions may undergo DNA repair, cause cell death, or be replicated during cellular functioning; the latter process being a first step for chemical carcinogenesis. Id.

Oxidative DNA damage occurs as a result of interactions between highly reactive oxygen species and DNA. Id. at 48-49. Reactive oxygen species (ROS's) are a byproduct of leaky energy conversion systems in many essential cellular functions. See Dennis V. Parke, The Cytochromes P450 and Mechanisms of Chemical Carcinogenesis, 102 ENVIRON. HEALTH PERSPECT. 852 (1994). The most reactive ROS is the hydroxyl radical produced by the Fenton Reaction involving oxidation of a reduced transition metal in the presence of hydrogen peroxide. See Irwin Fridovich, Superoxide Dismutases: An Adaptation to a Paramagnetic Gas, 264 J. BIOL. CHEM. 7761 (1989). Hydroxyl radicals directly react with DNA resulting in damage to proximal DNA structures. See Clayson & Iverson, supra, at 48-49. Oxidative DNA damage measured in vivo in adult rats has been estimated at 1 million lesions per genome, however, mammalian cells are highly evolved to deal with oxidative damage through specific DNA repair mechanisms and most oxidative DNA damage does not lead to neoplastic initiation. Id.

The third mechanism of chemical carcinogenesis is the increased development of naturally occurring background tumors. Id. at 49. Preneoplastic lesions arise naturally as a statistical inevitability of DNA repair mechanisms. Id. A relatively new field of cancer research is attempting to quantify increases in the development of these background lesions into actual neoplasms. The exact mechanism causing increased development is still unknown, but is suspected to be related to either electrophilic mechanisms or oxidative damage. Id.

A fourth mechanism for chemical carcinogenesis involves the interaction of specific substances with receptor proteins to form complexes that alter the expression genetic information. Id. at 49-50. Many of the substances identified as acting in this way have been associated with cellular proliferation in endocrine or endocrine-responsive cells. Id. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), the suspected carcinogenic contaminant of Agent Orange and the most potent rat chemical carcinogen known, is thought to act through this mechanism. Id.

83. Electrophilic interactions form DNA adducts comprised of an electrophilic molecule covalently bound to a nucleophilic moiety on a DNA strand. See David B. Clayson & Frank Iverson, Cancer Risk Assessment at the Crossroads: The Need to Turn to a Biological Approach, 24 REGUL. TOXICOL. PHARMACOL. 45, 48 (1996). Electrophilic interactions may occur spontaneously as a result of natural processes or the introduction of exogenous chemical compounds. Id. Adducts formed by electrophilic interactions may undergo DNA repair, cause cell death, or be replicated during cellular functioning; the latter process being a first step for chemical carcinogenesis. Id.

84. Pitot & Dragan, supra note 76, at 226.
85. Id. at 227.
endogenously or as a result of an exogenous carcinogen acting directly on DNA. Preneoplastic lesions occurring as a result of initiation are common in many systems and do not lead to neoplasia in the absence of the latter stages of development. The second stage, promotion, involves the proliferation of initiated cell populations. The final stage, progression, signifies the conversion of non-intrusive, benign neoplasms into malignant neoplasms. Progression is the most recognizable event in cancer development and is characterized by expression of genetic damage typically manifested by abnormal metastatic growth, tissue invasiveness, hormonal responsiveness, and morphological characteristics. Initiation, promotion, and progression are highly interrelated and may occur as the result of contact by a carcinogen capable of eliciting all three responses or through contact with multiple carcinogens each capable of eliciting a separate response.

The critical concept of cancer development is its dynamic nature: each stage is interrelated and involves a statistical probability of progression to the next stage. Understanding the dynamic nature of chemical carcinogenesis enables one to better understand the monumental task faced by risk assessment as it attempts to quantify the risks posed by pesticides. It also demonstrates why the Delaney Clause is outdated in relation to pesticides. Carcinogenesis is a complex process involving many variables. When viewed in this way, many chemicals are carcinogens; however, few are complete carcinogens capable of causing cancer development in the absence of other aggravating factors. Approximately 50 percent of chemicals tested in laboratory animals are found to have some carcinogenic activity, while scientists within the National Toxicology Program estimate that as few as 10-15 percent of these actually pose a realistic threat. Therefore, bright-line rules such as the Delaney Clause are unrealistic and inconsistent with modern science.

86. Id.
87. Id. at 227-30. Promotion differs from initiation in that it is a reversible process and does not require direct interaction with DNA. Id. Typically, promotion occurs as a result of expression of proto-oncogenes which enhance cellular proliferation of initiated cells, or through repression of the expression of tumor suppressor genes which cause apoptosis of initiated cells. Id. at 234-35.
88. Id. at 230.
89. Id.
B. Cancer Risk Assessment

The unrealistic nature of the Delaney Clause has forced a shift in risk regulation that calls upon science to synthesize gathered data to produce realistic quantifications of risk. Much like the FQPA's approach to the crossroads in law, science is facing its crossroads by moving away from bright-line techniques to more realistic, flexible methods. Science is bridging the gap between discovery and synthesis with adaptable approaches to risk assessment that recognize past changes in scientific knowledge and prepare for inevitable future changes.

Risk assessment begins with the fundamental nature of the risk being quantified. Quantifying risk is typically a task of handling dynamic and evolving information. Examining the current and future trends in risk assessment demonstrates that risk assessment is an adapting science. Risk assessors recognize the flaws in their methods and are constantly attempting to improve their science through new and better techniques. Cancer risk assessment illustrates this well.

Current cancer risk assessment begins with the use of statistical models developed from our understanding and lack of understanding of cancer development. A theoretical safe dose of a carcinogen is assumed to be nonexistent. Exposure to one carcinogenic molecule may presumably lead to cellular initiation and eventually a malignant neoplasm.\(^91\) The theoretical risk of this occurring for a carcinogen of moderate potency has been calculated at about 1 in \(10^{19}\).\(^92\) This theory has led to the development of dose-response curves for tumor incidence that are based on animal bioassays (usually chronic, 2-year studies) carried out at a Maximum Tolerated Dose.\(^93\) The data from animal bioassays is fit to a curve, the shape depending on the chosen model, and the theoretical response to a given dose is then extrapolated from the curve. The one-hit hypothesis or linear model for cancer risk assessment assumes that dose results in a linear response.\(^94\)

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\(^91\) See Pitot & Dragan, supra note 76, at 255.
\(^92\) See Clayson & Iverson, supra note 84, at 50. To further illustrate, assuming a world population of 5 billion and a mean generation time of 20 years, exposure of every individual to one molecule of the carcinogen would lead to cancer once every \(10^{11}\) generations or \(2 \times 10^{12}\) years. Id.
\(^94\) See Pitot & Dragan, supra note 76, at 255. In a dose-response curve, dose is the independent variable and is represented by the X-axis and response is the dependent variable.
Extensions of this model include the multi-hit model which factors in the need for multiple events to occur for malignant cancer development and the Linearized Multistage model ("LMS") (adopted by EPA). LMS models incorporate theories of multiple stages of cancer development into a statistical approach to risk quantification. Prominent among these models is the Armitage and Doll approach which is capable of incorporating one aspect of pathogenesis into a model that assumes irreversibility of progression from one stage to the next. Gaining more recent attention, the Moolgavkar two-stage model factors biological processes such as cell proliferation and apoptosis into a two-stage linear model. Such linearized dose-response models can then be used with exposure assessments to develop statistical lifetime risk estimates. These estimates typically employ a 95 percent upper confidence interval to the calculated risk to decrease the likelihood of model failure.

Despite these efforts, however, current cancer risk assessment continues to be plagued by a lack of information. We still do not fully understand the dynamics of cancer development, and consequently, quantifying the risks associated with chemical carcinogens is a monumental challenge. Current practices are hampered by information gaps in dose-response curves, insufficient physiological and biochemical information, incomplete knowledge of cancer development, and inability to measure actual exposures. These information gaps force risk assessment to utilize default assumptions in an attempt to accurately portray risks. The greater the use of

and is represented by the Y-axis. A linear response is a straight-line dose-response curve. In linear multi-stage models, a straight-line curve is still present, but the slope of the line typically changes from stage to stage. Id.

95. See NATIONAL RESEARCH COUNCIL, SCIENCE AND JUDGMENT IN RISK ASSESSMENT 65 (1994) [hereinafter SCIENCE AND JUDGMENT].
96. See Pitot & Dragan, supra note 76, at 255.
97. Id. at 225; See also Suresh H. Moogavkar & E. George Luebeck, Incorporating Cell Proliferation Kinetics into Models for Cancer Risk Assessment, 102 TOXICOLOGY 141, 142-43 (1995).
98. See Pitot & Dragan, supra note 76, at 255; See also SCIENCE AND JUDGMENT, supra note 95, at 65.
99. See Graham, supra note 90, at 41-45.
100. The current cancer risk assessment models rely heavily upon several inherent assumptions. Among these assumptions are: (1) results at high doses in animal bioassays may be linearly extrapolated to low dose exposures; (2) rodent bioassay results are relevant to human populations; (3) there is no threshold dose for chemical carcinogens. See Pitot & Dragan, supra note 76, at 254-57. Default assumptions are used for the uniformity, completeness, and clarity they provide risk assessment. SCIENCE AND JUDGMENT, supra note 95, at 86-87. But, when applied unilaterally they fail for a variety of reasons.
default assumptions, the more risk assessment models become, like the Delaney Clause, rigid methods too often arbitrary and unrealistic.

To deal with the inadequacies of current cancer risk assessment, new, more flexible approaches are being created. Physiologically based pharmacokinetic ("PBPK") models represent a scientific advancement rapidly being developed to cope with such inadequacies. The use of this method may greatly improve projection of risks by

The first assumption, that high-dose test results may be extrapolated to low-dose exposures, fails for several reasons. Experimental results at high doses are relatively easy to quantify for many carcinogens and test species. But, as doses decrease substantially and begin to drop to the small doses actually encountered in the environment, experimental results quickly become cloudy or completely lacking. See Cohen, supra note 93, at 79. For some carcinogens, DNA mutations at the cellular level become the only means of quantifying results. As demonstrated earlier, quantification at this level is doomed to inaccuracy because of endogenous DNA repair systems and cellular apoptosis. See Clayson & Iverson, supra note 83, at 46; SCIENCE AND JUDGMENT, supra note 95, at 86-87. Another problem arises in the case of nongenotoxic carcinogens which typically act as promoter agents without acting directly upon DNA. A primary example of model failure under these circumstances occurs with sodium saccharin, a nongenotoxic carcinogen that experimental evidence has shown to be carcinogenic only in rats treated at high doses. No experimental basis for low dose linear extrapolation has ever been shown. See Cohen, supra note 93, at 77-79. Finally, linear extrapolations to low doses do not typically account for changes in pharmacokinetics (relating exposure to dose) and pharmacodynamics (relating dose to response) that occur in extrapolating high dose responses to low dose exposures. See Graham, supra note 90, at 42.

The second assumption, that animal rodent bioassays are relevant to human populations fails in some cases because physiological differences between humans and rodents lead to complete breakdowns of experimental models. One well-known case involves chemicals found in wholly volatilized unleaded gasoline which induce male rat-specific renal tumors through a male rat-specific α-globulin. See Clayson & Iverson, supra note 83, at 45; Graham, supra note 90, at 42. Another key problem with animal bioassays is the use of MTD's in experimental designs. MTD's tend to cause metabolic saturation of tissues and organs resulting in abnormal metabolism and clearance of cellular constituents. This tends to lead to increased cellular proliferation and genotoxicity. Both of these consequences have been implicated as major factors in cancer development. See Clayson & Iverson, supra note 83, at 46-48; SCIENCE AND JUDGMENT, supra note 95, at 65-67. A third problem with animal bioassays is illustrated by the case of vinyl chloride showing an opposite failure of animal bioassays where the human cancer risk of this chemical is thought to be substantially higher than that associated with laboratory studies. SCIENCE AND JUDGMENT, supra note 95, at 65-66. The use of animal bioassays to assess cancer risk is, at best, a qualitative tool that may be used to identify possible human carcinogenicity.

The third major default assumption in current cancer risk assessment models, that no thresholds exist for cancer development, is false, as demonstrated by naturally-occurring background tumors that fail to develop into malignant neoplasms. Further support of threshold doses is being supplied by research into DNA repair mechanisms. The body produces DNA damaging agents endogenously as part of cellular functioning and, in response, has evolved mechanisms specially equipped to cope with this damage. Experiments suggest that DNA repair capacity is inducible and, therefore, capable of responding to increases in DNA damage or ROS production. See Clayson & Iverson, supra note 83, at 48-49; Cohen, supra note 93, at 852-53.
integrating highly complex systems into models that can assess an abundance of factors and variables.

PBPK models are based on biological rate constants, partition coefficients, and physiological parameters of exposed and test animals as well as the pharmacokinetics and pharmacodynamics of the test compound. This information is used to develop chemical concentration and time-course predictions for specific tissues and organs. PBPK models are capable of integrating biological, chemical, and physiological data to produce models that can be effectively extrapolated to human exposures at actual doses. Such models are capable of processing large amounts of mathematical and biological data to produce more accurate dose-response curves at high and low doses. PBPK models have even been created using magnetic resonance imaging (MRI) to generate three-dimensional physiological images that can be incorporated into risk assessment models.

PBPK models allow for interspecies extrapolations by substituting default assumptions with more appropriate parameter values for the species of interest. Once a model is developed, computerized simulation of possible exposure scenarios can be quickly performed to estimate corresponding risks. PBPK models minimize the need for dependence upon default assumptions in models, thus reducing the uncertainty associated with the models and resultant risk assessment. In addition, these models allow the development of well-defined, experimentally-based dose-response curves that are far more accurate than current dose-response curves. The problems associated with PBPK models stem from the need for intricate knowledge of a chemical’s biochemistry and metabolism and of an organism’s physiology. Additionally, identifying all of the parameters needed to accurately depict a real-world scenario is a time-consuming and costly task. Undoubtedly, as our body of scientific

101. See John Nichols et al., Three-Dimensional Visualization of Physiologically Based Kinetic Model Outputs, 102 ENVIRON. HEALTH PERSPECT. 952 (1994); Melvin E. Andersen & Kannan Krishnan, Physiologically Based Pharmacokinetics and Cancer Risk Assessment, 102 (Supp. 1) ENVIRON. HEALTH PERSPECT. 103 (1994).
102. Andersen & Krishnan, supra note 101, at 103-04.
103. See Nichols et al., supra note 101, at 952-55.
104. See Andersen & Krishnan, supra note 101, at 103-04.
105. See id. at 104.
106. See id.
107. See id.
108. See id. at 107.
knowledge continues to grow at a rapid pace, these problems will gradually be overcome.

Finally, chemical carcinogenesis and cancer risk assessment are illustrative of many other difficulties that regulatory toxicology faces as it reaches the crossroads in science. The FQPA mandates developmental risk assessments to measure risks to infants and children, an area as complex and rapidly-evolving as chemical carcinogenesis. Such an area will undoubtedly see the same influx of information and creation of more sophisticated risk assessment models as discussed for chemical carcinogenesis. Already, embryologically-based dose-response models similar to PBPK models are being developed. These models specifically address the physiological and toxicological effects of contaminants on fetuses and infants.

In sum, regulating toxicological risks tends to be complex and highly interrelated, and risk assessment models are rapidly evolving to more effectively deal with these problems. Enactment of the FQPA changes the law's approach to the regulation of pesticides. The decision has been made to replace the Delaney Clause's bright-line rule regarding carcinogenic risk with a more flexible science and economics based risk-benefit analysis. Simultaneously, we are also at a turning point in science. Laws such as the FQPA force science to bridge the discovery and understanding phase of research with a data synthesis phase to produce quantifiable risk estimates. Current risk assessment models have failed to accurately portray risks associated with environmental exposure to carcinogens, resulting in the undue regulation of some compounds and inadequate regulation of other compounds. Consequently, risk estimates have shown as much as a 10,800-fold exaggeration of risk, eroding public confidence in risk assessment. PBPK and similar models present the possibility of incorporating the dynamic nature of disease development into

109. Food Quality Protection Act of 1996 § 408(b)(2)(C), Pub. L. No. 104-170, 110 Stat. 1489, 1517-18 (1996). A recently published study indicates infants consume 3-4 times more food on a body weight basis than adults and, additionally, their food sources tend to be far less diverse. The result is an increased susceptibility to some environmental factors that is not correctly accounted for in many risk assessments. B. Schilter et al., Limits for Pesticide Residues in Infant Foods: A Safety-Based Proposal, 24 REGUL. TOXICOL. PHARMACOL. 126, 126-27 (1996) (supporting the use of a ten-fold safety factor where toxicological data is limited, especially regarding neurotoxic effects).


111. Clayson & Iverson, supra note 84, at 46.
mathematical models better equipped to quantify risks. The end product is risk assessment that is adaptable to changing science and capable of adequately portraying danger in a manner that will allow our society to economically allocate resources to deal with 'real' risks instead of 'possible' risks. The final question becomes: How should the regulatory process operate at the crossroads in science and law?

III. CHALLENGES FOR THE REGULATORY STATE.

The challenges confronting the regulatory process in the face of the changes in science and law are monumental. The FQPA will cause significant changes in the functioning of EPA and its responsibilities as a regulatory agency. EPA already faces tremendous challenges in other regulatory arenas and the FQPA will only add to these. As a result, recognizing the crossroads in science and law and ensuring that the regulatory process can cope with these inherent changes is imperative for EPA to succeed in the future.

The ultimate success of EPA and the regulatory process hinges on the ability to handle evolving science and law. Success at the regulatory level requires effective regulatory analysis and improved risk communication. Effective regulatory analysis depends on the adaptability, efficiency, and ability of regulators to handle changing science and produce quality regulations well-grounded in sound science, economics, and law. Improved risk communication depends on the establishment of a leader for the regulatory process who will be trusted and can serve as an icon of risk analysis, guiding public perceptions toward creation of a safer society.

A. Effective analysis

Effective regulatory analysis hinges on the abilities of the corps of regulators performing the analysis. In the case of pesticide residues, and in regulatory toxicology in general, the regulatory process must be highly adaptable and staffed by multi-disciplinary regulators who can perform efficient analyses.

The need for a highly adaptive regulatory process is grounded in the fundamental nature of the risk being regulated. Toxicology and risk assessment are sciences, and regulatory toxicology cannot escape that science. Economic analyses and risk-benefit decisions are only
as good as the science upon which they are based. Therefore, the need for a highly adaptive regulatory body is grounded in science. Science is evolving and, therefore, undergoes constant change. The logical conclusion for regulatory toxicology is that it must be equally adaptive and dynamic in order to process and effectively analyze risks originating in a changing scientific world.

Greater regulatory adaptability may lie in the more flexible statutory language of the FQPA. The Delaney Clause contained rigid language that left the regulatory process little room to maneuver. Consequently, the regulatory process has been unable to effectively adapt to changes in toxicology and risk assessment. The National Research Council called for Delaney Clause reform in 1987. The FQPA finally delivered some semblance of that reform in 1996. Nine years of misallocated resources filled the interim. In addition, the National Research Council in 1993 recognized the special dangers of pesticides in the diets of infants and children, yet it took three years for the FQPA to be passed allowing the regulatory process to finally act upon this new knowledge.

More flexible statutory language should produce a more adaptive and dynamic regulatory process that is able to implement sound scientific evidence more easily and prevent years of misallocated resources and unregulated risks.

Second, regulatory analysis must be performed by well-qualified, multi-disciplinary individuals. Skill in economic, policy, and scientific analysis is critical for effective analysis in regulatory toxicology. Foremost among these skills is the need for well-qualified scientists. Science is the foundation of regulatory toxicology; all other analyses build on this foundation. Sound science must be at the heart of any reform of regulatory toxicology.

112. Gio Batti Gori reminds us of the need for valid scientific truth in policy-making and states that “generalizations based on reductionist models are not value-neutral but a matter of opinion and therefore the instrument of special interest. When presented as established fact, they become an obvious menace to freedom and fairness, in both public and private policies.” Gio Batta Gori, The Role of Objective Science in Policy Development: Evidence versus Conjecture, 24 REGUL. TOXICOL. PHARMACOL. S3, S5-S6 (1996).

113. See discussion supra pp. 403-06.

114. See discussion supra pp. 406-09.

115. See supra note 43.

116. See NATIONAL RESEARCH COUNCIL, UNDERSTANDING RISK: INFORMING DECISIONS IN A DEMOCRATIC SOCIETY 24 (Paul C. Stern & Harvey V. Fineberg eds., 1996) [hereinafter “UNDERSTANDING RISK”].

117. See id.; see also John Cady, FDA Reform: The Need for a Sound Science-Based Approach, 51 FOOD & DRUG L.J. 407, 407-08 (1996). Cady specifically deals with FDA reform and argues for change that will encourage creativity and flexibility that allows adaptation to
however, is not a purely scientific endeavor. Economic and policy training are equally important. 118 Building on a strong foundation of scientific research will make economic analyses more reliable and will result in a better regulatory process. 119 Multidisciplinary regulators capable of discerning good economic cost-benefit analyses built on strong science could take a more holistic approach to the regulatory process and produce more effective regulation. 120

Finally, regulatory analysis must be efficient. Richard Pildes and Cass Sunstein report that our nation spends as much as $400 billion dollars per year on regulation. 121 A substantial portion of this is spent on regulatory toxicology. The current system is criticized for being ineffective at allocating resources and appropriately setting priorities for research and regulation. This has resulted in an inconsistent regulatory process. 122 Part of the problem is a regulatory process (EPA included) that is far too bureaucratic and chaotic with little integration among agencies or even regulations. 123 Regulators taking a more holistic approach to the regulatory process could eliminate many of the communication breakdowns and tie-ups that often occur within a large bureaucracy. Such regulators could have more control over scientific methods and allocation of resources changing science. He denounces the FDA’s need to establish advisory panels to make decisions on new food additives and argues instead for more efficient alternatives for making scientific decisions such as third-party review. 118 at 408. Cady’s argument can easily be applied to EPA’s responsibilities to oversee pesticide residue regulation.

118. Science is indispensable to risk analysis, but is not the lone component of good risk decisionmaking. Public choices, economic impacts, and legal implications must all be considered as parts of the risk problem. See UNDERSTANDING RISK, supra note 116, at 24-26.


120. Holistic Risk Assessment (HRA) is an emerging theory in environmental decisionmaking and is defined as “the process of integration of several nonsequential steps that tabulate and express risk factors and choices for both human and ecological systems through comparative integration.” Terence Harvey et al., Holistic Risk Assessment: An Emerging Process for Environmental Decisions, 22 REGUL. TOXICOL. PHARMACOL. 110, 111 (1995). HRA ties together human health and ecological risk characterizations and includes steps from chemical or hazard identification all of the way through risk communication. See id. Use of this process can help to facilitate efficient and more appropriate allocation of resources. See id. at 114.


122. See BREYER, supra note 24, at 10-29; Sunstein, supra note 119, at 257-60.

123. See Pildes & Sunstein, supra note 121, at 3-4 (stating that national bureaucracies are too numerous and regulations are too independent resulting in inconsistency within the regulatory process).
and would be better equipped to eliminate wasteful and unproductive regulation that consumes valuable time and resources. The result would be a more efficient and cost-effective regulatory process.

B. Improved Risk Communication

The crossroads faced by science and law contain many gray areas and difficult choices. The nature of some of these choices cannot be easily communicated to the public because of expert disagreements and a lack of reliable scientific results. However, many of the choices, such as Delaney Clause Reform, have had overwhelming expert and industry support for years. As such situations arise, expert and industry consensus must be successfully communicated to the public at large.

EPA has recognized that successful risk communication is an integral part of the process of assessing and analyzing risk. The National Research Council concluded that “it is mistaken to expect improved risk communication to always reduce conflict and smooth risk management . . . . But even though good risk communication cannot always be expected to improve a situation, poor risk communication will nearly always make it worse.”

Currently, public perceptions of risk and expert perceptions of risk are divergent. Risks associated with pesticides illustrate this well. A 1987 survey of women, college students, activists, and experts ranking the perceived risk for thirty activities and technologies showed concern over pesticides ranking as high as fourth and as low as fifteenth with experts ranking them as eighth. This demonstrates the varying degrees of concern that different segments of our

124. Such regulators could facilitate effective identification of how research resources need to be allocated. Government must place a high premium on accurate information and regulators fueled by this intent must seek the best data they can find. Sunstein, supra note 119, at 264. At times the private sector can best fulfill this need where competition for government research resources may act as an incentive to produce accurate and reliable scientific data. See id. (acknowledging the need to gather information from the private as well as public sectors and criticizing the current regulatory process for failing to create incentives to produce accurate data.); Cady, supra note 117, at 408 (stating “[s]cientific expertise does not reside only within the agency [FDA] . . . . Reform measures must look outside of the agency to accelerate the pace of review.”)


126. NATIONAL RESEARCH COUNCIL, IMPROVING RISK COMMUNICATION 3 (1989) [hereinafter “IMPROVING RISK COMMUNICATION”].

127. BREYER, supra note 24, at 34.
society have regarding pesticide risks. Mustering support for risk management is difficult when perceived risk varies greatly among affected parties.

Such fragmented goals are highly detrimental to the regulatory process. Legislative acts such as the FQPA depend on public and expert support for successful implementation at the regulatory level. A regulatory process torn between regulating the public’s perceived risk and accomplishing the often distinctly different goal of producing a safer society is ineffective. A regulatory process with limited resources cannot accomplish such divergent goals and must use risk communication to produce more synchronistic goals. Such synchronicity could be partially accomplished by the establishment of a leader for the regulatory process who can help build public trust and can serve as an icon of risk analysis and guide public perceptions. This risk communicator could help re-establish confidence in the regulatory process and unify public and expert risk perceptions.

A risk communicator faces a difficult task in unifying expert and public risk perceptions. Justice Breyer leaves little hope for such an endeavor:

It is hard to make the normal human mind grapple with this inhuman type of problem. To change public reaction, one would either have to institute widespread public education in risk analysis or generate greater public trust in some particular group of experts or the institutions that employ them. The first alternative seems unlikely. The second, over the past thirty years, has not occurred.128

While Justice Breyer’s statement about generating greater public trust correctly identifies the solution, establishing such trust remains problematic.

Justice Breyer’s solution is worth exploring in the context of EPA. Trust is a critical factor in risk communication.129 Problems with our current regulatory efforts point to a lack of trust in govern-

128. Id. at 39.
129. See L.I. Frewer et al., What Determines Trust in Information About Food-Related Risks? Underlying Psychological Constructs, 16 RISK ANALYSIS 473, 473 (1996) (stating that trust in information about food-related risks may be viewed as being as important as the content of the information.); Paul Slovic, Perceived Risk, Trust, and Democracy, 13 RISK ANALYSIS 675, 675 (1993).
ment regulation as being a major causal element. \textsuperscript{130} If we do not trust government agencies and administrators, whom do we trust?

Recent research shows that we place a high degree of trust in physicians and little trust in government and industry officials. \textsuperscript{131} This conclusion is probably not shocking to most readers. Currently, it is hard for the public to identify with EPA. It is a large bureaucratic organization headed by an Administrator. There is little with which those outside of government can identify. One way to correct this would be to establish an EPA Surgeon General recruited from the medical and toxicology fields. We all deal with doctors. We know them and interact with them. And, for the most part, we trust them. \textsuperscript{132} An EPA Surgeon General could be symbolic of the work being conducted at the agency. He or she would be viewed as a leader and could assume the position of a primary risk communicator.

Establishing such a position could have several advantages. First, since an EPA Surgeon General would be an individual with specialized medical training, he or she would be competent to discuss the human health aspects of the risk they are dealing with. Such skills add greatly to the credibility of a risk communicator. \textsuperscript{133} Second, as a medical professional, he or she would be more trusted than someone from a non-medical field. Third, since the EPA Surgeon General would have a primary goal of public communication, he or she would be visible and identifiable to the public. Fourth, an EPA Surgeon General would be a unifying voice of EPA, helping eliminate conflicting risk communication. Finally, he or she would be the keystone in building confidence and support for risk communication at the upper levels of government management. The outcome would be greater acceptance of and emphasis on risk communication at all levels of government. An EPA Surgeon General would be capable of establishing the public support needed to modify legal relics such

\textsuperscript{130} Slovic, \textit{supra} note 129, at 676.

\textsuperscript{131} See Frewer et al., \textit{supra} note 129, at 481-84 (presenting the results of two surveys in England which both ranked medical doctors as the most trustworthy sources of risk information and ranked government ministers and members of parliament as the least trustworthy sources of risk information); Slovic, \textit{supra} note 129, at 676 (contrasting our relatively high degree of trust in physicians administering potentially risky X-rays and medicines with our relatively low degree of trust in government officials overseeing management of nuclear power and nonmedical chemicals).

\textsuperscript{132} See Frewer, \textit{supra} note 129, at 481-84; Slovic, \textit{supra} note 129, at 676.

\textsuperscript{133} See \textsc{Improving Risk Communication}, \textit{supra} note 126, at 124-25.
as the Delaney Clause, thus adding to the adaptability and efficiency of the regulatory process.

Certainly, fulfilling the requirements of the position outlined above would be a monumental task. Trust is a fragile commodity that is difficult to build and easy to destroy.134 This only makes the task of an EPA Surgeon General more difficult, but few tasks within regulatory toxicology are easy. This is the price we pay for a technologically advanced society. Hopefully, in time, an EPA Surgeon General could re-establish our society's trust in regulatory toxicology and unify the dual objectives of regulating publicly-perceived risks and accomplishing actual public safety.

CONCLUSION

The FQPA represents a crossroads in both science and law. A fundamental shift in how the law approaches risk regulation is occurring. The FQPA replaces the rigid statutory language used by the Delaney Clause to regulate pesticide residues in processed foods with a more flexible science-based approach. The more flexible approach will give EPA more freedom and responsibility to act in the face of scientific change. Simultaneously, the FQPA requires science to extend its traditional goals of discovery and understanding to the more synthetic goals of accurately evaluating information and quantifying risks. The end result of the FQPA is an EPA and a regulatory process poised on the verge of tremendous change.

The extension of scientific responsibilities will give EPA the chance to develop and institute more accurate risk assessment models to more precisely define risks. The discovery of multiple stages and pathways in chemical carcinogenesis has greatly changed the way we view cancer and cancer risk. This new knowledge of cancer's dynamic nature has led to the development of physiologically-based risk assessment models capable of dealing with such dynamic concepts. EPA must recognize such innovative technologies and allocate sufficient resources to continue developing new, more accurate risk assessment models.

If we ignore the momentous changes occurring in science and law, the consequences may be serious. Failure of EPA to act decisively and efficiently under the freedom of flexible laws such as

134. See Slovic, supra note 129, at 676-78 (discussing the nature of trust in relation to human psychology).
the FQPA will force a reversion to rigid statutory language that specifically dictates EPA's course of action. Concurrently, failure of EPA to develop and adopt more effective risk assessment models that make use of state of the art understandings of risk etiology will result in inaccurate and dangerously misleading risk estimations.

EPA must acknowledge its position at the crossroads. At the regulatory level, EPA must adopt adaptable methods, multi-disciplinary approaches, and efficient analyses that will guarantee effective functioning. EPA must also improve its risk communication with the public to ensure awareness of EPA's position and rebuild trust and credibility in the agency. The end result will be a credible, more unified EPA seeking goals that the public understands and supports.

By ignoring the role it plays in changing science and law, EPA will continue to fall prey to criticisms of ineffectiveness and incompetence. The regulatory process will become increasingly difficult and riddled with faults. Resources will continue to be misallocated and society's demand for a safer environment will not be adequately met. EPA will become a straw house battered by the increasingly strong winds of change that are inevitable in our modern world.