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The Food Quality Protection Act—Implementation and Legal Challenges

by Lynn L. Bergeson and Carla N. Hutton

The U.S. Congress enacted the Food Quality Protection Act (FQPA)[1] in 1996. In so doing, Congress revolutionized the fundamental principles of food safety and ushered in a new regulatory and legal framework for addressing food safety issues. The legal, regulatory, and scientific challenges posed by the U.S. Environmental Protection Agency's (EPA's) and other federal agencies' implementation of the FQPA poses unprecedented opportunities and pitfalls for the legal practitioner and toxicologist.

This Article introduces the FQPA, and describes chemical substances for which testing could be conducted under the FQPA, chemical testing that could be required, persons required to conduct the tests, procedures that have been considered for selecting test chemicals, and associated legal challenges.

The FQPA

In 1996, as a result of the FQPA amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA),[2] EPA gained additional responsibility to regulate pesticides. The FQPA revised the FFDCA and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).[3] The major FQPA amendments to the FFDCA include: (1) health-based safety standards for pesticide residues in food; (2) special provisions for infants and children; (3) limits on "benefits" considerations; (4) review of all existing pesticide tolerances by the year 2006; (5) uniformity of tolerances; and (6) screening and testing for endocrine disruption.[4] Specific FQPA amendments to FIFRA include: (1) pesticide reregistration is required every 15 years; (2) EPA is required to develop procedures for expedited review of safer pesticides; (3) provisions to facilitate "minor use" registrations; and (4) requires EPA to expedite the review and registration of antimicrobial pesticides.[5]

The FQPA requirements related to screening and testing for endocrine disruption and establishing tolerances (maximum permissible pesticide residue limits on treated food) are described below.

Chemical Substances

Section 405 of the FQPA states that in carrying out the program, the EPA Administrator:

> (A) shall provide for the testing of all pesticide chemicals; and (B) may provide for the testing of any other substance that may have an effect that is cumulative to an effect of a pesticide chemical if the Administrator determines that a substantial population may be exposed to such substance.[6]

Pesticide chemicals include active pesticide chemicals and inert formulation ingredients. Substances that may have an effect that is cumulative to an effect of a pesticide chemical are those substances that have a "common mechanism of toxicity." The term common mechanism of toxicity did not exist in the prior version of the FFDCA, and was subject to a range of potential scientific definitions. EPA defined the term to mean two or more pesticide chemicals or other substances causing a common toxic effect to human health by the same, or essentially the same, sequence of major biochemical events, or mechanisms.[7]

Chemical Testing

Under the FQPA, pesticide chemicals and substances that may have an effect that is cumulative to an effect of a pesticide chemical must be included in a program that includes screening and testing for endocrine disruption and establishing tolerances.

Persons Required to Test

EPA is authorized to require testing by registrants, manufacturers, and importers.[8] If a registrant fails to comply with a test order, EPA can issue a notice of intent to suspend, which will be final after 30 days unless the registrant has fully complied or requests a hearing.[9] Any other person who fails

Lynn L. Bergeson is a founding shareholder of Bergeson & Campbell, P.C., a Washington, D.C., law firm concentrating on industrial, agricultural, and specialty chemical and medical device product approval and regulation, product defense, and associated business issues. Carla N. Hutton is with Bergeson & Campbell, P.C.

1. Pub. L. No. 104-170, 110 Stat. 1489 (1996).
2. 21 U.S.C. §§301-397.
3. 7 U.S.C. §§136-136y, ELR STAT. FIFRA §§2-34.
4. FQPA §405; *see also* U.S. EPA, *The Food Quality Protection Act (FQPA) Background: FQPA Amendments to FFDCA*, *at* http://www.epa.gov/oppfead1/fqpa/backgrnd.htm#ffdca (last updated May 8, 2003).
5. FQPA §§106, 210, 224, and 250; *see also* U.S. EPA, *The Food Quality Protection Act (FQPA) Background: FQPA Amendments to FIFRA*, *at* http://www.epa.gov/oppfead1/fqpa/backgrnd.htm#fifra (last updated May 8, 2003).
6. FQPA §405(p)(3).
7. U.S. EPA, "Pesticides: Glossary" ("Two or more chemicals or other substances that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (*i.e.*, interpreted as mode of action)"), *at* http://www.epa.gov/pesticides/glossary/#c (last updated Aug. 4, 2003); *see also* U.S. EPA, GUIDANCE FOR IDENTIFYING PESTICIDE CHEMICALS AND OTHER SUBSTANCES THAT HAVE A COMMON MECHANISM OF TOXICITY 4 (1999), *available at* http://www.epa.gov/fedrgstr/EPA-PEST/1999/February/Day-05/6055.pdf.
8. FQPA §405(p)(5)(A).
9. *Id.* §405(p)(5)(C)(i).

to comply will be subject to penalties and sanctions under §16 of the Toxic Substances Control Act (TSCA).[10] Since EPA has yet to implement endocrine disruption testing, no one has challenged the FQPA testing requirements.

Selecting Chemicals for Endocrine Disruption Testing

In May 1996, EPA sponsored a workshop to: (1) discuss development of a screening and testing scheme for endocrine-disrupting chemicals; and (2) obtain public comment on the need to organize the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC). Following the May workshop, EPA's Office of Prevention, Pesticides, and Toxic Substances (OPPTS) established the EDSTAC, which was chartered in October 1996, under the Federal Advisory Committee Act (FACA). The FACA requires that advisory committees have a balanced representation of public interest groups so that no individual interest group predominates, and that all official advisory committee meetings be open to the public.

The EDSTAC developed a conceptual framework to screen and test chemicals for endocrine disruption for implementation by EPA's OPPTS. To assist the EDSTAC in developing this conceptual framework, the EDSTAC created the Priority Setting Work Group and the Screening and Testing Work Group. To communicate development of its conceptual framework to the public, the EDSTAC created the Communication and Outreach Work Group. To learn of public concerns and incorporate them into the conceptual framework, the EDSTAC convened public workshops in San Francisco, California; Houston, Texas; Baltimore, Maryland; Chicago, Illinois; East Elmhurst, New York; Orlando, Florida; and Washington, D.C., from December 1996 to June 1998. Under the FQPA, EPA was required to:

> develop a peer-reviewed screening and testing plan by August 1998;
>
> implement screening and testing by August 1999; and
>
> report progress on screening and testing to Congress by August 2000.[11]

The FQPA requires EPA to screen and test pesticide chemicals and substances that may have an effect that is cumulative to an effect of a pesticide chemical for estrogen disruption related to human health effects. At its first meeting, the EDSTAC expanded the scope of its deliberations to include potential effects of chemicals on the androgen and thyroid systems in addition to estrogen disruption. The EDSTAC cited numerous examples of anti-androgen and anti-thyroid agents and the impact that androgen and thyroid systems have on reproduction, growth, and development as reasons for their inclusion. Ecological effects were also deemed important in that ecological effects have provided the strongest evidence of endocrine disruption to date. Finally, the EDSTAC also included chemicals other than pesticides as candidates for screening and testing. The universe of candidate chemicals under consideration numbers about 87,000, including: approximately 900 pesticide active ingredients; 2,500 pesticide formulation inert ingredients; 75,500 industrial chemicals; and 8,000 cosmetics, food additives, and nutritional supplements. EPA adopted the EDSTAC's recommendations as the basis of its proposed Endocrine Disruption Screening Program (EDSP).[12]

During the December 1997 EDSTAC meeting in Orlando, Florida, Version 1 of the Endocrine Disruption Priority Setting Database (EDPSD v.1) was presented. EDPSD v.1 was developed as a tool that could be used to assist rapid sorting and priority setting of chemicals for endocrine disruption screening and testing.[13]

Version 2 of the Endocrine Disruption Priority Setting Database (EDPSD v.2) is a multiuser client/server application developed using Visual Basic 6.0 for the front-end screens and user interface, Microsoft Access97 for the back-end database, and Seagate Crystal Reports 7 for the reports. A user's guide is available for EDPSD v.2.[14] The structure and functions of EDPSD v.2 have been described previously.[15]

Implementing Chemical Endocrine Disruption Testing

To implement testing, EPA proposes to: (1) sort chemicals into groups; (2) establish screening priorities; (3) require Tier 1 screening; and (4) require Tier 2 testing. Chemicals may be sorted into four groups: (1) polymers with a numerical average molecular weight greater than 1,000 daltons and exempted chemicals, which are pesticides given an exemption under FFDCA §408(p) and other chemicals that EPA determines to be exempt from the requirements of screening; (2) chemicals for screening to estimate their potential for endocrine activity; (3) chemicals that have sufficient data to bypass screening, but need testing; and (4) chemicals with adequate data to perform hazard assessments.[16] EPA plans to use Tier 1 screening to identify chemicals that have potential to produce effects through an endocrine disruption mode of action and Tier 2 testing to characterize and quantify those effects by providing dose-response data and to establish whether a chemical disrupts endocrine systems.

EPA asked the Science Advisory Board (SAB) and Scientific Advisory Panel (SAP) to review the proposed EDSP, as described in EPA's December 28, 1998, *Federal Register* notice. The SAB/SAP Joint Subcommittee made several recommendations, including that EPA implement the EDSP on 50 to 100 compounds and submit the data to independent review to eliminate methods that do not work and thus optimize the EDSP.[17] On December 30, 2002, EPA released its proposed chemical selection approach for the initial round of screening.[18] EPA would select and screen approximately 50 to 100 chemicals drawn from pesticide active ingredients

10. §405(p)(5)(D); 15 U.S.C. §§2601-2692, ELR STAT. TSCA §§2-412.

11. §405(p)(1), (2), and (7).

12. U.S. EPA, Endocrine Disruptor Screening Program; Proposed Statement of Policy, 63 Fed. Reg. 71542 (Dec. 28, 1998).

13. John D. Walker, *Applications of QSARs in Toxicology: A U.S. Government Perspective*, 622 J. MOLECULAR STRUCTURE—THEOCHEMISTRY 167-84 (2004).

14. U.S. EPA, *Draft User's Guide for the Endocrine Disruptor Priority Setting Database (Version 2 Beta)* (May 22, 2000), at 1-1, *at* http://www.ergweb.com/endocrine/edpsdug.pdf.

15. John D. Walker, *QSARs for Endocrine Disruption Priority Setting Database 2: The Integrated 4-Phase Model*, 22 QSAR & COMBINATORIAL SCI. 89-105 (2003).

16. 63 Fed. Reg. at 71546-47.

17. U.S. EPA, REVIEW OF THE EPA'S PROPOSED ENVIRONMENTAL ENDOCRINE DISRUPTOR SCREENING PROGRAM 32 (1999), *available at* http://www.epa.gov/science1/pdf/ec13.pdf.

18. 67 Fed. Reg. 79611 (Dec. 30, 2002).

and high production volume (HPV) chemicals with some pesticidal inert uses (HPV/inert chemicals). EPA does not intend to develop an ordinal ranking of priorities of the chemicals within this initial list.

EPA proposed using several bodies of data to identify pesticide active ingredients for screening in the first use of the Tier 1 battery. These data focus on human exposure by different pathways:

> as a consequence of consumption of food containing pesticide residues;
>
> as a consequence of consumption of drinking water containing pesticide residues;
>
> as a consequence of residential use of pesticide products; and
>
> through occupational contact with pesticide-treated surfaces.

For each of the four pathways, EPA identified existing data that it believes will help to identify active ingredients likely to be among those having either relatively more widespread or higher levels of human exposure than would be expected for other active ingredients. EPA proposed giving higher priority for inclusion on the list for initial screening to chemicals likely to have human exposure via multiple pathways, with the highest priority being given to substances having exposure through all four pathways.

EPA proposed using a generally similar approach to identify HPV/inert chemicals to be included in the initial list for screening in the Tier 1 battery. According to the *Federal Register* notice, EPA generally has more extensive information of known quality available to assess potential exposure to pesticide active ingredients via food, water, occupational, and residential exposure pathways than is available to assess exposure to HPV/inert chemicals. In addition, EPA generally has more extensive information available on usage (including both agricultural and residential) of active ingredients than is available for HPV/inert chemicals (including both pesticidal and nonpesticidal uses of those same substances). For these reasons, the specific data and approaches EPA identified for selecting an initial set of HPV/inert chemicals differs somewhat from those proposed for selecting pesticide active ingredients. For HPV/inert chemicals, EPA will focus on several indicators of the potential for human exposure, including production volume, specific pathways of exposure, and presence in human tissues:

> First, EPA will review existing databases to identify chemicals that are both pesticide inerts and HPV (defined as chemicals that are manufactured or imported into the United States for all uses in amounts equal to or greater than one million pounds per year) chemicals. This first step will focus initial Tier 1 screening of pesticide inerts on chemicals with higher potential human exposure on the basis of large amounts produced or imported each year in the United States.
>
> Second, EPA will review existing data to identify HPV/inert chemicals that have been found to be present in: human tissue, ecological tissues that have human food uses, i.e., fish tissues, drinking water, and/or indoor air. Using this approach, an HPV/inert chemical appearing in monitoring data from one or more of these media would be a higher priority for testing than an HPV/inert chemical that does not appear in monitoring data from any of the media.

Following consideration of comments on this draft approach, EPA will issue a second *Federal Register* notice setting forth its approach for selecting the first group of chemicals and the chemicals it proposes for this initial list. Following comment on the draft list of specific chemicals, EPA will issue the final list. EPA stresses that, because the list of chemicals produced using the proposed approach will be a list of chemicals that EPA, in its discretion, has decided should be tested first, based primarily upon exposure potential, it should not be construed as a list of known or likely endocrine disruptors nor characterized as such. EPA anticipates that it will modify its chemical selection approach for subsequent Tier 1 screening lists based on experience gained from the results of testing of chemicals on the initial list, the feasibility of incorporating different categories of chemicals, e.g., nonpesticide substances, and additional pathways of exposure, and the availability of new priority-setting tools.

Tier 1 screening assays are intended to:

> 1. maximize sensitivity which serves to minimize false negatives;
> 2. include a range of organisms representing differences in metabolism;
> 3. detect all known modes of action for the endocrine endpoints of concern;
> 4. include a sufficient range of taxonomic groups among the test organisms; and
> 5. incorporate sufficient diversity among the endpoints, permitting weight-of-evidence conclusions.

Tier 1 screening may include:

> *In Vitro* Assays:
>
> Estrogen Receptor Binding/Reporter Gene Assay;
>
> Androgen Receptor Binding/Reporter Gene Assay; and
>
> Steroidogenesis Assay With Minced Testis.
>
> *In Vivo* Assays:
>
> Rodent 3-Day Uterotrophic Assay;
>
> Rodent 20-Day Pubertal Female With Thyroid;
>
> Rodent 5-7-Day Hershberger Assay;
>
> Frog Metamorphosis Assay; and
>
> Fish Gonadal Recrudescence Assay.

Alternatives for Tier 1 screening include:

> *In Vitro* Assay:
>
> Placental Aromatase Assay.
>
> *In Vivo* Assays:
>
> Modified Rodent 3-Day Uterotrophic Assay (Intraperitoneal Dosing);
>
> Rodent 14-Day Intact Adult Male Assay With Thyroid; and
>
> Rodent 20-Day Thyroid/Pubertal Male Assay.

A weight-of-evidence approach is being considered for evaluating Tier 1 screening results and making decisions about proceeding to Tier 2 testing. This approach would include: (1) the balance of positive and negative responses observed in both the *in vitro* and *in vivo* assays; (2) the nature and range of the biological effects observed; (3) the shape of the dose-response curves; (4) the severity and magnitude of effects induced; and (5) the presence or absence of response in multiple taxa.

For chemicals that proceed to Tier 2 testing, there must be a need to determine whether a chemical exhibits endocrine-mediated adverse effects and to identify, characterize, and quantify those effects. To be effective for Tier 2, tests must: (1) include the most sensitive developmental lifestage; (2) identify the specific hazard caused by the chemical and establish a dose-response relationship; and (3) include a range of taxa. With these criteria in mind, the following tests may be incorporated into Tier 2:

Two-Generation Mammalian Reproductive Toxicity Study;
Avian Reproduction Test;
Fish Life-Cycle Test;
Mysid Life-Cycle Test; and
Amphibian Development and Reproduction Test.

To implement any of the procedures, screens, or tests described above, EPA may use a variety of approaches. The FQPA provides EPA with order authority to implement screening and testing.[19]

Legal Challenges

Since its enactment, the FQPA has had a few legal issues challenging attorneys. The FQPA's enactment has changed fundamentally the legal landscape for lawyers practicing in the pesticide area. The FQPA has imposed tremendous burdens on EPA to implement provisions in the Act by dates certain. EPA has chosen to discharge its obligations by creating a new framework to implement the requirements of the Act. The framework consists of the issuance of science policy papers that EPA has been careful to specify are guidance documents and not rules. As such, the more traditional notice-and-comment opportunities provided under the Administrative Procedure Act (APA),[20] and all of the attendant opportunities for judicial challenge of final agency action arguably are not applicable.

This new implementation paradigm has inspired tremendous concern, debate, and litigation. EPA's alleged failure to satisfy certain statutory deadlines arising under the FQPA have also been the subject of litigation. On August 3, 1999, for example, the Natural Resources Defense Council, Inc. (NRDC) and six environmental organization co-plaintiffs filed suit in the U.S. District Court for the Northern District of California alleging that EPA failed to reassess, as mandated by the FQPA, the riskiest one-third of all tolerances and failed to implement and enter a screening program by August 3, 1999.[21] Also in the summer of 1999, the American Farm Bureau Federation (AFBF), CropLife America (then the American Crop Protection Association), and seven other agricultural industry groups sued EPA in the U.S. District Court for the District of Columbia, requesting that EPA issue regulations governing the issuance of FIFRA §18 exemptions and that EPA follow its statutory requirements in assessing and reassessing protection products under the FQPA.[22] The industry groups asked EPA to update its regulation specifying the information EPA needs, utilize data call-in procedures rather than rely on defaults, theoretical models, and assumptions, publish a revised schedule for tolerance reassessment, and implement notice-and-comment rulemaking rather than informal and draft policies in choosing a percentile of acute dietary exposure (99.9%) and determining appropriate FQPA safety factors (10x).

In January 2001, the NRDC and EPA proposed a settlement of both lawsuits.[23] The proposed settlement included a consent decree binding EPA to deadlines for completing reregistration eligibility decisions (REDs) and risk assessments, and a settlement agreement containing flexible target dates for completing development of a database that EPA would use to prioritize chemicals for screening in the EDSP, completing validation of the screens and tests that would be part of the EDSP, and starting to require screening and testing of chemicals under the EDSP. On January 19, 2001, the NRDC and EPA filed a motion asking the court to enter the proposed consent decree into the record, thus making it enforceable against EPA. The industry intervenors, who were not included in the settlement discussions, opposed the proposed consent decree and asked the court to order EPA to publish it in the *Federal Register* for public comment. On April 13, 2001, the court ordered EPA to solicit public comment on the proposed consent decree and proposed settlement agreement. On April 27, 2001, EPA published the proposed consent decree and proposed settlement agreement on its website.[24]

On September 25, 2001, the California district court approved the consent decree, which established deadlines for completing REDs for four pesticides, interim REDs for six pesticides, and a cumulative risk assessment for organophosphate pesticides, and for determining whether two groups of pesticides share common mechanisms of toxicity and whether three pesticides pose risks to workers constituting unreasonable adverse effects on the environment.[25] In its order, the court found that the proposed settlement terms were "fair, equitable, reasonable, legal, and in the public interest." The court approved the consent decree, which set the following deadlines for risk assessments, REDs, and interim REDs:

RED for propargite—September 30, 2001;
Interim RED for chlorpyrifos—September 30, 2001;

19. FQPA §405(p)(5)(A).
20. 5 U.S.C. §§701-706.
21. Natural Resources Defense Council v. Browner, No. C99-3701 (N.D. Cal. Aug. 3, 1999).
22. American Farm Bureau Fed. v. EPA, No. 99-01405 (D.D.C. Oct. 30, 2000).
23. Settlement Agreement (Jan. 19, 2001), *at* http://www.epa.gov/scipoly/oscpendo/docs/settlement.pdf.
24. U.S. EPA, *Request for Public Comment on Consent Decree Involving Pesticide Tolerance Reassessment and Pesticide Reregistration*, *at* http://www.epa.gov/oppfead1/cb/csb_page/updates/nrdc-comt.htm (last updated May 15, 2001).
25. Natural Resources Defense Council v. EPA, No. C99-03701 (N.D. Cal. Sept. 25, 2001), "Order Approving Proposed Consent Decree; Dismissing Count Six of Complaint Brought by NRDC *et al*., Dismissing Complaint Brought by AFBF, *et al*."

EPA must make its "best efforts" to complete interim REDs for phosmet and azinphos methyl by October 15, 2001, but must finish by no later than October 30, 2001;

REDs for benomyl, endosulfan, and lindane—July 31, 2002;

Interim RED for diazinon—July 31, 2002;

Interim RED for atrazine—August 3, 2002;

Interim RED for carbaryl—June 30, 2003; and

Revised risk assessment for metam-sodium—August 31, 2004.

Under the consent decree, EPA was also required to meet the following deadlines:

conduct and solicit public comment on a preliminary cumulative risk assessment for organophosphate pesticides by December 1, 2001;

conduct a revised cumulative risk assessment for organophosphate pesticides within 240 days of the preliminary risk assessment;

initiate regulatory action within specified times after completion of interim REDs for chlorpyrifos, azinphos methyl, and diazinon if worker risks are found to cause unreasonable adverse effects;

determine whether common mechanisms of toxicity exist for thiocarbamates and dithiocarbamates by December 31, 2001, and for triazines by March 31, 2002, and solicit public comments on these determinations; and

publish an annual report discussing progress toward completing reregistration and tolerance activities for certain chemicals.

In its September 25, 2001, order, the court noted that the consent decree "explicitly reserves [plaintiffs'] rights to challenge any final agency action," contains provisions that allow noncompliance with certain deadlines if EPA determines that its premises or methodology are "significantly flawed," and includes sections "that allow EPA to delay certain decisions if it is provided with new scientific information." The court overruled industry objections that it lacked jurisdiction, stating that it had jurisdiction under the APA.

On September 15, 2003, two lawsuits were filed in the U.S. District Court for the Southern District of New York against EPA claiming that EPA has not complied with the FQPA's requirements to protect children from pesticides. The NRDC filed suit against EPA for failing to comply with legal requirements to protect children, farm workers, and the general public from allegedly dangerous pesticides under the FQPA.[26] The NRDC asked the court to force EPA to comply with the FQPA's key provision requiring the Agency to protect infants and children 10 times more stringently than adults, unless it can show that children do not have special sensitivities. The states of Connecticut, Massachusetts, New Jersey, and New York filed the second suit against EPA, claiming that EPA has not complied with the FQPA to protect children from pesticide residues.[27]

The NRDC lawsuit charges that EPA has violated the law by:

failing to use a tenfold infant and child protection safety factor;

failing to protect highly vulnerable or highly exposed people, including farmworkers' children and other children living on or near farms, who are more heavily exposed to pesticides than average children; and

relying on a confidential, proprietary, industry-developed computer model to determine pesticide risks.

On February 6, 2004, EPA filed motions to dismiss both cases for lack of subject matter jurisdiction. On April 9, 2004, the court granted the plaintiffs' motion to consolidate the cases. Clearly environmental groups such as the NRDC intend to continue to sue EPA seeking to enforce the provisions of the FQPA.

To be eligible for registration, a food-use pesticide must meet the tolerance standards of §408 of the FFDCA, as amended by the FQPA. EPA cannot issue a pesticide registration for a food-use chemical unless it also establishes a tolerance—a maximum permissible pesticide residue limit—on the treated food. EPA's implementation of the FQPA has changed radically the legal standards for establishing tolerances, leaving EPA with the important task of giving precise scientific definitions to the new legal standards. To accomplish this task, EPA has engaged in a complete review and rethinking of its tolerance-setting science policy. Several of the major science policy decisions reached at this interface of science and law are discussed below.

Safety Standards

One basic task confronting EPA was to define the terms in the new safety standard. Under FFDCA §408(b)(2)(A), a tolerance can only be set if EPA finds that the tolerance is "safe," defined by the FQPA to mean "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."[28] Aggregate exposure refers to dietary exposure under all tolerances established for the pesticide, as well as exposure from all nonoccupational sources (for example, drinking water) and the cumulative effects of the pesticide residues "and other substances that have a common mechanism of toxicity."[29]

The term common mechanism of toxicity did not exist in the prior version of the FFDCA, and was subject to a range of potential scientific definitions. EPA has settled on an ap-

26. Natural Resources Defense Council v. Horinko, No. 1:03-CV-07176 (D. Md. Aug. 20, 2003). On March 30, 2004, the court granted the February 27, 2004, motion to intervene filed by Captain Task Force, Makhteshim-Agan of North America, Inc., Syngenta Crop Protection Inc., Monsanto Company, Gowan Company, Ltd. Liability Corporation, Bayer CropScience Ltd. Partnership, and CropLife America. As of May 21, 2004, 10 environmental groups have intervened as co-plaintiffs.

27. New York v. EPA, No. 1:03-CV-07155 (N.Y. Sept. 15, 2003). On March 30, 2004, the court granted the February 27, 2004, motion to intervene filed by Syngenta Crop Protection Inc., Monsanto Company, E.I. DuPont de Nemours and Company, Bayer CropScience Ltd. Partnership, and CropLife America.

28. FQPA §405(b)(2)(A)(ii).

29. *Id.* §405(b)(2)(D); *see also* U.S. EPA, General Principles for Performing Aggregate Exposure and Risk Assessments (2001), *available at* http://www.epa.gov/pesticides/trac/science/aggregate.pdf.

proach which defines the term to mean that two or more pesticide chemicals or other substances cause a common toxic effect to human health by the same, or essentially the same, sequence of major biochemical events, or mechanism. A common toxic effect is the same toxic effect in or at the same organ or tissue.[30] By limiting the term common mechanism of toxicity to mean an effect produced by the same mechanism of action in the same target organ or body tissue, EPA has avoided an overly broad definition which could lead to the cancellation of a significant number of existing pesticide registrations. This approach is a good example of the use of science policy to shape legal criteria.

Safety Factors

Another key legal standard which needed scientific definition was the application of the FQPA safety factor. Under the FQPA, EPA must make a specific determination that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide.[31] In this evaluation, EPA must consider available information on the disproportionately high food consumption of a commodity by infants and children, any special susceptibility of infants and children to the pesticide, and the cumulative effects on infants and children of the pesticide and "other substances that have a common mechanism of toxicity" with the pesticide.[32] An additional tenfold margin of safety must be applied to the reference dose (RfD) to take into account "potential pre- and post-natal toxicity and completeness of the data" with regard to infants and children.[33] Dietary risk is a function of toxicity and dietary exposure.[34] EPA typically expresses the toxicity portion of the risk equation as the RfD, in units of milligrams per kilogram of body weight per day (mg/kg body weight/day). An RfD represents the amount of a substance to which a person can be safely exposed in a day.[35] Typically, to determine the RfD, EPA divides the no observed adverse effect level (NOAEL) from an animal study by a safety factor.[36] For animal data, the safety factor is usually 100.[37] If the RfD is derived from human data, a safety factor of 10 is typically used.[38] EPA can dispense with the extra tenfold margin of safety, in whole or part, if EPA determines "on the basis of reliable data" that the lesser safety factor will be safe for infants and children.[39]

This legal standard required the development of a new scientific policy defining "reliable data." The choice of policy had critical ramifications for the continued registerability of many food use pesticide products. In developing its policy, EPA first determined the applicable legal framework: the FQPA safety factor is directed solely at uncertainty resulting from incompleteness of the data and EPA has the discretion, on a case-by-case basis, to apply a lower or higher uncertainty factor than the default tenfold FQPA factor, depending on the completeness of the database.[40] To define the completeness of the developmental toxicity database, EPA developed the concept of a core toxicology database. The term "developmental toxicity" is defined as "adverse effects on the developing organism that may result from exposure prior to conception (to either parent), during prenatal development, or postnatally to the time of sexual maturation."[41]

A debate of more recent origin involves the appropriateness and relevance of human testing data. EPA's initial position was that human test data will not be relied upon to establish a no observed effect level (NOEL). This position was based on a November 1999 SAP and SAB joint meeting at which it was determined that human data should not be relied upon to establish an NOEL for FQPA purposes.[42] In December 2001, EPA announced that it had asked the National Academy of Sciences (NAS) to review the scientific and ethical issues posed by EPA's possible use of third-party studies using human subjects.[43] EPA also announced that it would not consider or rely on any human studies in its regulatory decisionmaking, whether previously or newly sub-

30. U.S. EPA, Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity 3 (2002).

31. FQPA §405(b)(2)(C)(ii)(I); *see also* General Principles for Performing Aggregate Exposure and Risk Assessments, *supra* note 29; U.S. EPA, Exposure Data Requirements for Assessing Risks From Pesticide Exposure of Children (1999), *available at* http://www.epa.gov/scipoly/sap/1999/may/10xdoca3.pdf.

32. FQPA §405(b)(2)(C)(i); *see also* U.S. EPA, Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (2002), *available at* http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf.

33. FQPA §405(b)(2)(C); *see also* U.S. EPA, Standard Operating Procedures for the Health Effects Division FQPA Safety Factor Meeting (1999), *available at* http://www.epa.gov/scipoly/sap/1999/may/sop_hed.htm; U.S. EPA, Draft Toxicology Data Requirements for Assessing Risks of Pesticide Exposure to Children's Health (1999), *available at* http://www.epa.gov/scipoly/sap/1999/may/10xtx428.pdf; Exposure Data Requirements for Assessing Risks From Pesticide Exposure of Children, *supra* note 31.

34. U.S. EPA, Guidance for Refining Anticipated Residue Estimates for Use in Acute Dietary Probabilistic Risk Assessment (2000), *available at* http://www.epa.gov/pesticides/trac/science/residues.pdf.

35. U.S. EPA, Office of Pesticide Programs' Policy on the Determination of the Appropriate FQPA Safety Factor(s) for Use in the Tolerance-Setting Process: Response to Public Comments 44 (2002), *available at* http://www.epa.gov/oppfead1/trac/science/fqpa_resp.pdf.

36. *Id*.

37. U.S. EPA, Consideration of the FQPA Safety Factor and Other Uncertainty Factors in Cumulative Risk Assessment of Chemicals Sharing a Common Mechanism of Toxicity—Draft Document 6-7 (2002), *available at* http://www.epa.gov/oppfead1/trac/science/consid_draft.pdf.

38. U.S. EPA, Is an Additional Uncertainty Factor Necessary and Appropriate to Assess Pre- and Post-Natal Developmental and Reproductive Effects in Infants and Children Exposed to Pesticides Thru Chronic Dietary Exposure? 13 (1996), *available at* http://www.epa.gov/opppsps1/fqpa/10xrev.pdf.

39. FQPA §405(b)(2)(C); *see also* Consideration of the FQPA Safety Factor and Other Uncertainty Factors in Cumulative Risk Assessment of Chemicals Sharing a Common Mechanism of Toxicity—Draft Document, *supra* note 37.

40. FQPA §405(b)(2)(C).

41. U.S. EPA, The Office of Pollution Prevention and Toxics' Proposed Test Battery for the Children's Health Testing Program (1999), *available at* http://www.epa.gov/oscpmont/sap/1999/may/oppt_test.htm.

42. U.S. EPA, Comments on the Use of Data From the Testing of Human Subjects (2000), *available at* http://www.epa.gov/sab/pdf/ec0017.pdf.

43. U.S. EPA, Agency Requests National Academy of Sciences Input on Consideration of Certain Human Toxicity Studies; Announces Interim Policy (2001), *available at* http://www.epa.gov/epahome/headline2_121401.htm.

44. *Id*.

mitted.[44] CropLife America and several pesticide manufacturers filed suit in the U.S. Court of Appeals for the District of Columbia Circuit against EPA, arguing that the EPA directive in the press release was unlawful because it constituted a binding regulation that was issued without a notice of proposed rulemaking and opportunity for public comment, as required by the FFDCA.[45] The court agreed, and on June 3, 2003, the court issued its decision that EPA's December 14, 2001, press release constituted a "binding regulation issued without notice and the opportunity for comment."[46] The court further held: "The consequence is that the agency's previous practice of considering third-party human studies on a case-by-case basis, applying statutory requirements, the Common Rule, and high ethical standards as a guide," will remain in effect "unless and until it is replaced by a lawfully promulgated regulation."[47]

On February 19, 2004, NAS' National Research Council (NRC) released its report recommending that intentional dosing studies in humans may be conducted and used for EPA regulatory proposes if certain conditions are met:

> studies must be necessary and scientifically valid, addressing important regulatory questions that cannot be answered with animal studies or other studies that do not involve human testing. They must be designed, conducted, and reported in a scientifically rigorous manner to ensure that they answer a specific research question;
>
> the possible benefits to society from such studies must outweigh any anticipated risks to participants;
>
> studies whose results would be used for the sole purpose of improving the scientific accuracy of EPA's established RfDs for humans, and that would not provide health benefits otherwise, would be justified only if there were no identifiable risks to participants, or if investigators could show with reasonable certainty that participants would not be harmed; and
>
> all of the recognized ethical standards and procedures for protecting the interests of study participants must be observed, including equitable selection and recruitment of human subjects, the obtaining of informed consent, and independent review of the scientific and ethical merits of a given study by an institutional review board (IRB) or its equivalent.[48]

Although the NRC's charge was directed to third-party human dosing studies, the NRC concluded that the ethical and scientific issues are fundamentally the same whether a human study is conducted by a third party or by EPA, and that the same basic framework should apply to both categories of studies. After the NRC's report was released, EPA stated that it may take months or longer before EPA will propose a formal policy. If EPA must make a decision on the use of third-party human data before it has developed a formal rule or policy, EPA intends to ask an SAB subcommittee to offer its advice. On May 7, 2003, EPA issued an advance notice of proposed rulemaking (ANPR) regarding its stated intent to engage in rulemaking about the criteria and standards EPA would apply regarding data from research conducted on human subjects.[49] EPA initiated the ANPR to determine whether it would consider or rely on research involving human subjects submitted by third parties. Comments on the ANPR were due by August 20, 2003.

As of this writing, EPA has yet to issue its final human testing policy. The utility and relevance of human testing may continue to be a legal issue that lawyers will confront in the evaluation of tolerance reassessment process. Each of these tolerance reassessments will need to be reviewed on a case-by-case basis, and few generalizations can be made with respect to the legal challenges that are likely to arise.

A study generally must meet three criteria to be included in the core database: (1) official testing guidelines or standard, well-documented protocols must be available; (2) the study must be a Tier 1 requirement under Rule 40, Part 158 of the Code of Federal Regulations, triggered by the results of Tier 1 or other existing studies, or required under a well-established registration or reregistration policy; and (3) there must be consensus in the scientific community that a body of evidence supports the utility of the study for understanding the potential human (including infants and children) hazard of the pesticide. As a default position, EPA's Office of Pesticide Programs (OPP) will require an additional database uncertainty factor if one or more of the key studies in the core database is missing or inadequate.

At present, there are five study types comprising the core database: two chronic toxicity studies (in the rodent and nonrodent), a multigeneration reproductive toxicity study, and two developmental toxicity studies (in different species). The present core database will be expanded from five studies to six if the requirement for a subchronic adult neurotoxicity study has been triggered, but data have not yet been submitted, reviewed, and found acceptable. Ultimately, the core database will include a total of eight studies with the revision of Rule 40, Part 158 of the Code of Federal Regulations to include a developmental neurotoxicity study, and acute and subchronic neurotoxicity studies in adult rats. A study type will not become part of the core database until the study is routinely required and EPA has developed the appropriate data evaluation expertise. During the interim period before a study type is added to the core database, an additional uncertainty factor is not automatically mandated by the absence of the study. The OPP's general practice has been to apply an FQPA uncertainty factor of threefold if one of these studies is missing and the full tenfold uncertainty factor where more than one study is missing.[50] Any residual concerns regarding the adequacy of the risk assessment will be addressed in the weight-of-the-evidence evaluation conducted during the risk characterization process. If there is a high level of confidence that the combined hazard and exposure assessment adequately protects infants and children, no default FQPA factor would be necessary. A low level of confidence in the combined assessment, and residual concerns, would lead to the application

45. CropLife Am. v. EPA, No. 02-1057 (D.C. Cir. June 3, 2003).

46. *Id.* at 3.

47. *Id.* at 13.

48. NRC, Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues (2004), *available at* http://books.nap.edu/catalog/10927.html.

49. 68 Fed. Reg. 24410 (May 7, 2003).

50. Office of Pesticide Programs' Policy on the Determination of the Appropriate FQPA Safety Factor(s) for Use in the Tolerance-Setting Process: Response to Public Comments, *supra* note 35, at 55.

of an appropriate FQPA uncertainty factor. This approach represents a good example of the key role that science policy can play in the implementation of a statutory standard. The science policy developed by EPA avoids any rigid application of the FQPA safety factor and assures that each pesticide will be evaluated on a case-by-case basis to determine if it meets the standards of the FQPA.