SYMPOSIUM

Food Safety: Risk Assessment Methodology and Decision-Making Criteria

William J. Brock,[1] Joseph V. Rodricks,[1] Alan Rulis,[2] Vicki L. Dellarco,[3] George M. Gray,[4] and Richard W. Lane[5]

[1] *ENVIRON Health Sciences Institute, Arlington, Virginia, USA*
[2] *Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, Maryland, USA*
[3] *United States Environmental Protection Agency, Office of Pesticide Program, Washington, DC, USA*
[4] *Harvard Center for Risk Analysis, School of Public Health, Boston, Massachusetts, USA*
[5] *Unilever Bestfoods, Englewood Cliffs, New Jersey, USA*

As our scientific technology grows, risk assessment methods become more complex and, therefore, open to greater scientific debate. Risk assessment has always been a part of the regulatory notification and approval process for foods. However, the methodologies applied to risk assessment and decision-making have become diverse, dependent on a number of features, including the areas of the world in which one operates, the need to use cumulative risk assessment for pesticides and other ingredients or alternative risk assessment considerations for evaluating nontraditional or bioengineered foods. Diverse institutional structures within a single federal regulatory authority may tend to lead to diversity in risk outcomes that creates policy decisions that complicate and confuse the risk management process. On top of this challenge, decisions become more complicated by the need to examine beneficial factors of foods rather than the adverse effects of foods and food additives. Foods are a complex mixture of ingredients. Regulatory groups recognize the need to use new approaches for evaluating the safety and risks associated with foods and food additives, and to do so in a timely manner. The United States Food and Drug Administration (US FDA) in its need to ensure standards of "reasonable certainty of no harm" continues to explore alternative means to be responsive to petitioners as well as continue to examine scientifically validated means, e.g., quantitative structure-activity relationship (QSAR), and computer-assisted programs, within the approval process to assist in the evaluation of risks. Another means to improve the risk management process would include the cumulative risk assessment of pesticides that will, no doubt, be the beginning of more intensive efforts to understand cumulative exposures and the inherent risks from multiple pathways of exposure. The passage of the *Food Quality Protection Act* (FQPA) resulted in developing additional risk assessment methodologies and approaches to assess the potential for multiple exposures and risks. Addressing the international criteria used in decision-making related to foods safety assessment has resulted in acceptable intake values for food ingredients for carcinogens and noncarcinogens that, in general, tend to be more stringent in the United States compared to Europe. Clearly, the need for harmonization of risk assessment criteria and the impact of the decision process on regulatory approvals and safety assessment is a future need for the continued assurances of food safety. The topics presented in this paper are based on a symposium held in November 2002 at the annual meeting of the American College of Toxicology.

Keywords ADI, Food Safety, Pesticides, Risk Assessment

Well over 500 years ago, a basic tenet of toxicology was stated that all substances are potentially toxic and that the dose differentiates toxic from "nontoxic." Since the days of Paracelsus, tremendous amounts of research and personal energy have been expended to further define this tenet in terms of risks associated with exposures to natural and man-made chemicals and physical agents. No group of substances has received greater attention than foods. In the United States, the assessment of the safety of foods goes back decades, with one of the first comprehensive regulations for the control of food safety being the 1906 *Food, Drug and Cosmetic (FD&C) Act* of the United States Food and Drug Administration (US FDA). Changes to this regulation and the development of other international regulations continue to address the safety of foods as the science of food toxicology and nutrition continue to evolve.

The need to assure the general public of the safety of foods becomes a basic principle of regulatory authorities worldwide.

Received 22 April 2003; accepted 9 July 2003.
This article is based on a symposium presented at the American College of Toxicology, November 2002, in Hershey, PA.
Address correspondence to Dr. William J. Brock, ENVIRON Institute for Health Sciences, 4350 N. Fairfax Dr., Suite 300, Arlington, VA 22203, USA. E-mail: wbrock@environcorp.com

International Journal of Toxicology, 22:435–451, 2003
Copyright © American College of Toxicology
ISSN: 1091-5818 print / 1092-874X online
DOI: 10.1080/10915810390251438

When addressing the subject of food additives, the Joint Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JEFCA 1965) stated at its first session that permitted additives should be subjected to continuing observation for possible deleterious effects under changing conditions of use and should be reappraised whenever indicated by advances in knowledge. Similarly, the FDA continues to improve its own practices and methods to assure the public of the safety of foods.

Food is a very complex mixture of chemicals, and food will vary in composition depending on region of the world or even time of year, i.e., holiday foods may represent a different complex mixture than normal, daily food. Considerations of public health dictate that, as a matter of principle, foods and particularly food additives should be of known composition and purity. For production of food additives, modern methods generally make it possible to produce chemicals of greater purity and uniformity by synthesis than is usually achieved by derivation from substances of natural origin. Toxicological evaluation, which is a costly and time-consuming procedure, must be related to the particular grade or quality of chemical intended for use in food. The adoption of specifications of purity of food additives provide one means of accurate identification of the additive for regulatory purposes and limit the known undesirable ingredients or contaminants to acceptable tolerance levels.

Over the last 10 to 15 years, the science of risk assessment in regulations has seen tremendous growth. This science has developed from the days when "back of the envelope" calculations appeared to be sufficient today where complex mathematical modeling is the accepted practice. Regardless of the risk assessment practice, evaluating the risks associated with a single chemical tends to result in reducing the potential for adverse health outcomes. However, a level of complexity to the risk assessment process occurs when evaluating complex mixtures, and where exposures to these mixtures differs markedly depending on regions, time of year, and other demographic differences.

In past years, a basic approach to regulation of foods and chemicals in the United States has been a "risk-based" approach. In contrast, Europe has often taken the approach of hazard identification as a means for regulatory control. In the shrinking world economy, having two distinct processes that are at times at odds with one another creates confusion and uncertainty with respect to commercialization of products, including food (Lofstedt and Vogel 2001). Furthermore, assessing direct and indirect additives as well as impurities, e.g., pesticides, that appear in food becomes problematic because the exposure assessment between regions will differ widely as will the final regulatory control based on regional differences in approaches to risk assessment.

In November 2002, the American College of Toxicology (ACT) sponsored a symposium that addresses many of the key features of international risk assessment towards foods, and the criteria included in the risk assessment process. The purpose of this paper is present the relevant information contained in that symposium and review the criteria utilized by regulatory authorities in making risk decisions. Furthermore, as part of this symposium, the question is raised about potential harmonization of these criteria and the impact on regulatory approvals and safety assessments.

ASSESSING AND MANAGING FOOD-RELATED HEALTH RISKS AND BENEFITS: SCIENTIFIC AND INSTITUTIONAL NEEDS FOR THE FUTURE (Joseph V. Rodricks)

Of all the risks to human health arising from the environment, none presents a greater challenge to our understanding than those associated with the consumption of foods. This sweeping conclusion is based on the adoption of the broadest possible view of health risks, taken to encompass the total burden of morbidity and mortality that can be related to food consumption.

Because of the immense chemical complexity of foods, and because so many food constituents confer health benefits as well as increased risk for a potential adverse outcome, the scientific methods now available to identify and measure overall health impacts are put to no greater test than when they encounter the enormous variety of products used for nourishment and gastronomic pleasure. Moreover, because the influence of food consumption on the health status of human populations is very large and is understood unevenly, the development and implementation of appropriate risk management programs is also seriously challenged. Because we do not ordinarily attempt to grasp the problem of food-related health risks and benefits in its entirety, its true scope and magnitude is often not appreciated.

The study of food-related health risks and benefits has been, for several historical reasons, fragmented in ways that hinder the search for systematic understanding, and this has contributed to inefficiencies in attempts to manage those risks. The diverse institutional structures now in place to manage food-related risks contribute to this fragmentation (Institute of Medicine [IOM] 1998). There may be much value in breaking out of the ways of thought that have created our current systems. Two broad theses seem supportable:

1. Scientific understanding will be most efficiently advanced by the adoption of a unified framework for organizing and assessing food-related health risks and benefits of every type. Achieving this goal requires, at a minimum, elimination of the scientifically obsolete divisions that now exist in the assessment of the various sources of food-related risks and benefits.
2. A scientifically strong and unified institutional structure is required to promote the framework, to track progress in understanding made under it, and to put into place public health and regulatory policies consistent with those advances in scientific understanding.

The major classes of food-related health risks and benefits are presented in Table 1. The table also describes the principal scientific methods used to study each class, and broad generalizations

TABLE 1

Classes of food constituents and contaminants and their known and potential health impacts (Rodricks 2000)

Class	Description	Methods used to study risks and benefits	Importance and source of risks	Known and potential health benefits
Nutrients	Macronutrients (supplying energy) and micronutrients.	Clinical/epidemiological. Major challenge to develop experimental models to study excessive intakes.	MAJOR IMPORTANCE Excessive energy, saturated fat intake; abusive intakes. Inadequate intakes may be highly significant for micronutrients.	MAJOR IMPORTANCE Essential for life. Levels in excess of recommended intake levels may prove to be beneficial. Expanded study expected.
Natural, non-nutritive constituents	Largest and chemically most diverse class.	Little systematic study, mostly experimental.	INSUFFICIENT KNOWLEDGE A reasonable conjecture is that they are at least moderately important.	INSUFFICIENT KNOWLEDGE Some appear to offer benefits, and many may not.
Intentionally introduced substances, direct and indirect	Food additives, GRAS substances. Pesticides, veterinary drugs, feed additives. Indirect additives.	Experimental studies, well developed. Clinical for macroingredients. Little epidemiological study.	MINOR IMPORTANCE Many substances introduced decades ago have not been studied using current experimental methods.	MINOR IMPORTANCE Some may provide benefits through pathogen reduction, preservation of foods.
Chemicals produced during processing, preparation	Reaction products from heating, irradiation, etc. Chemically very diverse.	Little systematic study, mostly experimental.	INSUFFICIENT KNOWLEDGE A reasonable conjecture is that they are of minor but not negligible importance.	INSUFFICIENT KNOWLEDGE Not expected to confer significant benefits.
Contaminants	Substances not expected to be present. Industrial and natural chemicals, biological organisms.	Several contaminants very well studied, many not. Epidemiological and experimental.	MODERATE IMPORTANCE Pathogens produce largest number of "countable" cases of food-related illnesses; most not serious or irreversible. Persistent, bioaccumulative chemicals are of concern.	INSUFFICIENT KNOWLEDGE Not expected to confer significant benefits.
Dietary supplements	Substances permitted under DSHEA to be sold as supplements.	Little systematic study. Epidemiological and experimental both possible.	INSUFFICIENT KNOWLEDGE Reasonable conjecture not possible. Little systematic study.	INSUFFICIENT KNOWLEDGE Many perceived as beneficial. Little systematic study, but increasing.
Alcoholic beverages	Ethanol *plus* many fermentation products.	Epidemiological studies extensive.	MAJOR IMPORTANCE Abusive intakes associated with mortality and morbidity.	MODERATE IMPORTANCE Range of low intakes to decrease risk of coronary heart disease.

regarding our state of knowledge regarding the risks and benefits of each. Our understanding of health risks is, on the whole, and except for the nutrients, much greater than our understanding of health benefits. Moreover, our understanding of health risks is highly uneven among the classes (Table 1). Interestingly, the least-studied class consists of a large number of natural, nonnutritive substances present in the many products included in the human diet. It might be claimed that these substances have received so little attention because our food safety laws place major emphasis on added substances and contaminants—a case of legislative and regulatory prerogatives driving science. Based on knowledge of the chemical structures of natural food constituents, the biological properties of the relatively few that have been studied, and their immense numbers, it seems likely that the impact of this class—both adverse and beneficial—on human health is substantial. Given the current research and commercial interest in the health benefits associated with many of these substances, it seems likely that new knowledge regarding this class will emerge in the years to come. Other, similar examples can be found in which the search for understanding has depended upon social and political rather than scientific factors. This is not necessarily inappropriate, but it helps to explain why our degree of understanding is so uneven.

As a general matter, health risks arising from food and patterns of food consumption consist of a few very large risks, most arising from nutrient and alcohol abuse that contribute in substantial ways to many of the major chronic diseases and causes of death (Woteki and Thomas 1992), a few risks of moderate size, and a large number of relatively small risks (Table 1). The assessment of these many sources of risk now takes place in diverse institutions, public and private, and responsibilities for their management are divided among several federal agencies (IOM 1998). This institutional fragmentation in science and policy-making may become increasingly problematic as understanding of risks and benefits evolves.

Improvements in the methods used to study health effects will increase understanding of food-related risks and benefits and, at the same time, introduce greater challenges to our capacity to assess overall public health impacts and to reach well-founded decisions that maximally protect public health in the most efficient way. The current and well-known framework for risk assessment is, nevertheless, adequate to accommodate these new challenges. It is also appropriate for the evaluation of benefits, which can be characterized as exposures leading to reduced risks. For benefits assessment, "hazards" are those health risks reduced by the chemical exposure, and the "dose-response" describes the relationship (which may take several different shapes) between the size of that exposure and the incidence or severity of the hazard. Efforts to establish recommended daily allowance (RDA) for nutrients, for example, rest upon the identification of the health hazards associated with inadequate intakes and examination of the decline in those hazards as doses increase from zero (IOM 1997, 2001).

Although the evaluation of benefits from foods has not traditionally been explicitly conducted under the risk assessment framework, its elements are identical to those comprising that framework. The specific methodological approaches used within the framework will vary according to the nature of the substance or agent and its health effect, but the general framework—the pathway from research to the presentation of results useful for decision-making—can and should be the same for all of the many sources of food-related risks and benefits (National Academy of Sciences [NAS] 1983, 1994).[1] Given the immense nature of the scientific challenge that emerges when the problem of food-related risks and benefits is, as it should be, looked at as a whole, nothing but a concerted effort to assess those risks within a consistent and uniform framework could possibly tell us where we stand and where we are heading.

Risk management is a decision-making and implementing activity. Such activities include decisions regarding the need to reduce or otherwise limit or control health risks associated with food constituents and contaminants, as those risks have been identified in the assessment process. Once control mechanisms are selected and placed into effect, effective risk management requires some means for ensuring that responsible parties comply and that the control strategy is otherwise effective. All of this is undertaken within the bounds set by applicable laws (Institute of Food Technologists [IFT] 1998).

Many tools are available to the risk manager. Enforceable standards or action levels, warnings, information labeling, and educational materials are all useful, depending upon the context and the nature of the risk under consideration. Educational materials and other forms of information are most appropriate for those risks that are largely under personal control (nutrient and caloric intake, alcohol consumption), whereas enforceable standards are generally used for situations (contaminants, additives, pesticide residues) over which individuals has little or no control. The Hazard Analysis and Critical Control Point (HACCP) programs of the FDA and the Food Safety Inspection Service represent another type of management tool (Food Safety and Inspection Service [FSIS] 1997). The introduction of benefits assessment will require new risk management strategies, focused on the provision of maximum benefits and minimum risks.[2]

Although different risk reduction and control strategies are appropriate for different types of food-related risks and benefits,

[1] An important limitation in current risk assessment methods is the absence of a common measure of risk, one that would allow comparison of the many different types of risks and benefits associated with exposures to the various constituents of food. Some efforts are now underway to deal with this problem, including those devoted to common measures of reductions in quality of life associated with different types of adverse health effects. The Global Burden of Disease Study (www.who.int/whr/en), for example, involved the use of the disability-adjusted life-year (DALY) as a common measure of different types of fatal and nonfatal diseases.

[2] It is doubtful that current laws can accommodate this type of management strategy for all classes of food substances.

there could be much value in seeking a consistent framework within which such risk management decisions are reached. Indeed, unless all sources and types of food-related risks and benefits are evaluated within such a framework, it is difficult to envision allocations of resources consistent with achieving the greatest degree of public health protection in the most economical way.

It is difficult to imagine achieving what has been described without a single, scientifically strong, regulatory and public health agency with responsibility for tracking evolving knowledge of food-related risks and benefits and for managing them. The risk assessment and management requirements are growing to be so complex and important that institutional fragmentation is a recipe for substantial inefficiencies and increasingly deficient public health protection.

The current fragmented system has developed under the influence of legal requirements and political and social preferences that have evolved over the past century (Francer, Jung, and Pak 1998). These influences have served us well, and the point is not that past decisions regarding priorities, resources, and institutional mechanisms for dealing with food-related risks were incorrect or misdirected, but rather that the system that has evolved from those many decisions is not well-equipped to cope with the broad and complex problems of the future. This conclusion is consistent with that reached by the Institute of Medicine in 1998 (IOM 1998), but is based more narrowly on the difficulties our current institutional system will have in dealing with rapidly evolving scientific complexity.

SAFETY ASSESSMENT OF FOOD INGREDIENTS (Alan Rulis)

Since the 1950s the FDA's food additive safety decision framework has proven to be a reliable means of reaching valid safety decisions on new food additive uses. The current safety assessment approach compares the "estimated daily intake" (EDI) of the additive via food to an "acceptable daily intake" (ADI) derived from appropriate toxicological safety studies, to determine if the proposed use of an additive falls within the statutory safety standard of "reasonable certainty of no harm." Although this approach has served well for many decades, the agency has recently been expanding the range of available safety analysis tools and regulatory procedures it applies to an ever wider range of new and different types of food entities.

The current food additive decision framework comprises a set of statutory standards and scientific principles by which the agency reaches safety decisions on new food additive uses. It operates under the authority of the *Food, Drug, and Cosmetic Act* (FD&C Act). The Act establishes both the *standard of data review* and the *standard of safety* for food ingredients. The standard of safety is a "fair evaluation" of all the data of record. The safety standard is a "reasonable certainty of no harm" of the intended use of the material. This requires that the agency assess whether it has received from the applicant adequately documented answers to appropriate questions of probative value. "Reasonable" implies that safety evaluations are to be based on a scientific foundation and factual information, are subject to critical analysis, and are supported by rational arguments, which in their totality, lead to a definitive decision. "Certainty" implies that the concept underlying this safety standard is at least in part a probabilistic one. As such, some residual uncertainty must always be tolerated. "No Harm" emphasizes that this is, in fact, the goal, where "harm" is *harm to health*. Thus, decisions made under this standard require the application of informed judgment to, and the weighing of, all the evidence of record to reach a science-based decision that ensures, with reasonable certainty, that there will be no harm to health of consumers resulting from the decision of new use of the material in food.

In essence, to reach conclusions in this framework the agency compares the EDI of an additive to the ADI derived from an analysis of appropriate toxicological studies and application of safety factors (uncertainty factors) to no-observable-adverse-effect levels (NOAELs) from those studies. When the EDI is determined to be numerically less than the ADI, the use can be said to be "within the circle of reasonable certainty of no harm" (Figure 1).

The FDA's guidance documents on toxicological testing for new food additive uses, most notably, is the so-called "Redbook," (FDA 1993). Much has been written by the agency about how to establish intake estimates for any given food additive use scenario, using both traditional and Monte Carlo modeling. Guidance on these areas is available on the FDA web site (www.cfsan.fda.gov).

Over the years, FDA has summarized existing data in its files on hundreds of additive approvals, and has been able to discern an overall quantitative relationship between the EDI and corresponding ADI for numerous situations. In one analysis

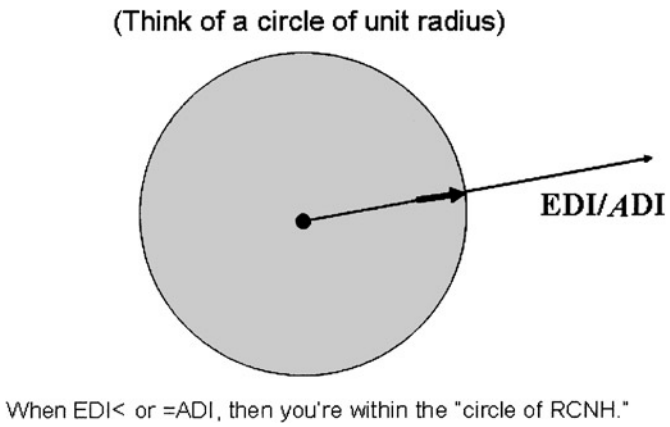

FIGURE 1

The "circle" of reasonable certainty of no harm (RCNH). When the numerical value of the estimated daily exposure to an additive is less than the acceptable daily intake, the use of the additive can be said to be within the circle of reasonable certainty of no harm, and thus safe within the meaning of the FD&C Act.

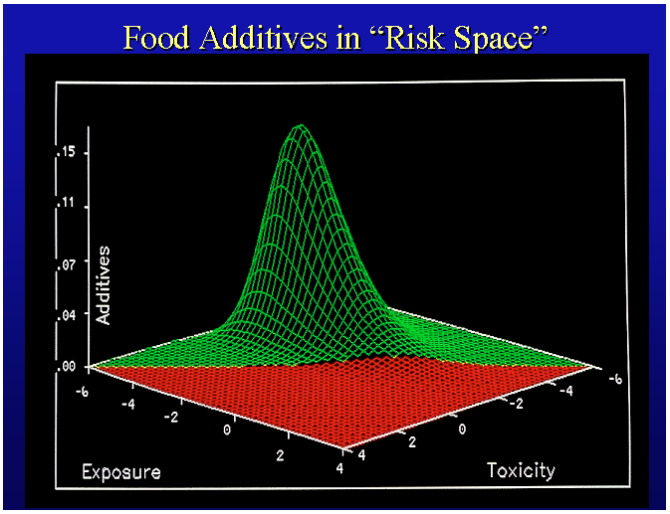

FIGURE 2
A three-dimensional distribution curve is used to describe the food additive exposures (mg/kg bw/day) and toxicities (approximate NOELs, in mg/kg bw/day) for a collection of approved food additives. For any given pair of exposure/toxicity values, the distance above the "Exposure-Toxicity" plane corresponds to the relative number of food additives with the corresponding pair of exposure/toxicity values. The exposure and toxicity axes are logarithmic, so the numerical values shown correspond to the exponents of the respective exposure and toxicity values. The color change in the plotted distribution represents roughly the demarcation line corresponding to NOEL-to-exposure ratios of 100-fold, where for the "lighter color" (*green*) region, the ratio is more than 100-fold (higher safety margin) and for the darker (*red*) region, less than 100-fold (lower safety margin).

(Figure 2; Rulis 1987), the agency simply fitted a smooth curve to the probability distribution of a collection of numerous food additive exposures (in mg/kg/day), and a separate curve to the distribution of numerous toxicological no-effect-level data in (mg/kg/day). Note in Figure 2 the relative number of additives associated with any given pair of exposure and toxicity values is represented by the (linear) vertical axis of the figure, whereas both the exposure and toxicity axes are logarithmic. The line of demarcation in this figure, roughly coincident with a factor of 100 applied to the NOAEL of the toxicological data, is shown by the color-shading change in the figure and is, when projected onto the exposure-toxicity plane, actually a straight line of unit slope. Figure 2 illustrates that current additive uses are, probabilistically, well within the EDI/ADI criterion, often by several orders of magnitude.

The traditional approach to reaching safety decisions on direct addition food additives has been expanded in recent years to incorporate new and different types of additives and uses not traditionally considered. For additives such as fat substitutes, for example, an ADI may not exist. Rather, FDA must focus on nutritional effects of the compound and on direct physiological effects in people. Thus, clinical data may become more important as do postmarket monitoring and active and passive surveillance for reports of adverse events. For safety evaluation of such substances, the ability to cause laxation in humans or to cause other gastrointestinal responses (e.g., bloating, cramps, vomiting, etc.) become foci. Also we must concern ourselves with potential adverse effects on nutrition such as vitamin and mineral absorption, etc. A good example of this type of expanded safety review beyond the EDI/ADI paradigm is the fat substitute olestra (Federal Register 1996).

FDA currently operates three new programs for evaluation of food ingredient safety. These are:

- Food Contact Substance Notification Program
- Bioengineered Foods Consultation Program
- GRAS Notice Program

The Food Contact Substances program came into being with the passage of the *Food and Drug Administration Modernization Act* (FDAMA) of 1997 and began when subsequent funding was made available. Food contact substances (FCS) are food packaging or other food contact materials that become components of food by virtue of migrating to food. Unlike direct food additives such as artificial sweeteners, for example, FCS are not intended to become components of food, but nonetheless fit the definition of a food additive. Notifiers for new uses of food contact substances will submit to the FDA the same types of exposure and toxicity information submitted under the previous premarket petition review process. Under FDAMA, however, the new uses of FCS may go on the market after 120 days unless the agency objects. Thus, the agency must review appropriate safety information and decide whether or not to object to the marketing of the substance. Since the program began in early 2000, FDA has received over 300 notifications for new uses of food contact substances and has a virtually 100% record of completing its safety reviews within the prescribed 120-day period.

The actual data analysis of the safety evaluation of FCS is handled in much the same way as for direct food additives. One difference is the frequent use of somewhat more detailed exposure calculations that may often require the modeling of diffusion of materials (possibly across barriers) into the food or into food simulating solvents. Otherwise, a traditional EDI/ADI analysis is invoked. Because of the expedited time frame for review, however, it is essential to reach early conclusions about the likely toxicity of any migrating entities into food. Increasingly, the agency is adopting the technique of chemical structure-analysis and (quantitative) structure activity relationships, (Q)SAR, analysis to assist in making inferences about the toxicity of individual chemical entities comprising a food contact substance, possibly in the absence of actual feeding study data.

During the first phase of FCS evaluation, FDA has been applying the Multicase and Oncologic expert systems and the

Toxsys database in its analysis. Beginning with a representative chemical structure, reviewers look for structural alerts to toxicological end points such as carcinogenicity or mutagenicity, and apply these findings to the safety review. In the final phases of the FCS evaluation, reviewers may search FDA's in-house databases for structural and functional analogs to the compound of interest and use available toxicity potency information, e.g., from the Carcinogen Potency Data Base (Gold and Zeiger 1997), to judge the likely upper-bound carcinogenicity risk of the subject compound or its impurities.

FDA published its current policy for handling the human health issues associated with bioengineered foods in the Federal Register (1992). This policy statement reviews the FDA's and industry's obligations under the FD&C Act and covers all methods of plant breeding, including those using recombinant DNA technologies, and applies to human foods such as fruits, vegetables, and grains, and applies as well to animal foods. An underlying premise of the policy is that most foods are accepted as safe based on experience, and thus premarket safety testing is not generally conducted on conventional foods. Today's food is the standard. New plant varieties are evaluated based on traditional counterparts in a multidisciplinary approach that includes attention to agronomic and quality characteristics, genetic, chemical, and nutritional analyses. If questions remain, toxicological testing may be invoked if there are, for example, novel or unusual proteins or other chemicals in the bioengineered plant, or if there are chemicals produced in the plant that have a similarity to known allergens or toxins. The goal is to assure that any new food produced using bioengineering is as safe as today's food.

Since the publication of its policy in 1992, FDA has held more than 80 consultations with prospective producers of bioengineered plant varieties. The first such consultation was for the Calgene tomato. About 50 consultations have been completed and have resulted in new crop plants reaching the marketplace. Most of these are for crop plants that contain new traits such as insect or herbicide resistance.

In response to public concerns, FDA conducted three public meetings on bioengineered foods in 1999. Subsequently, FDA published a Federal Register (2001a) proposal to make its bioengineered foods consultations mandatory as well as a Federal Register notice of availability of guidance on voluntary labeling of bioengineered foods (Federal Register 2001b). Over 100,000 comments were received on the proposal and are currently under review by the agency.

FDA published in the Federal Register (1997) a proposal to reform the process by which the agency reviews whether food ingredients uses are generally recognized as safe (GRAS), and to change FDA's approach to acknowledging independent determinations of GRAS status. Under the procedures proposed, FDA received approximately 120 GRAS notifications from interested parties who have independently asserted the GRAS status of a use of a food ingredient. As of October 2002, the agency has issued over 104 responses to these notices. FDA's responses are of three types and consisted of no questions by the FDA, the Notice does not provide a basis for GRAS or the notifier stops the process.

In keeping with the notion of general recognition as a public process, notifications to the agency and communications and responses from the agency ultimately end up on the agency's web site. To date the agency has responded to over 70% of GRAS notices in less than 180 days of receipt.

For many of the types of chemical entities and applications where GRAS status is sought, the range of types of evaluation is much broader than typically associated with food additives historically. These often include the so-called "macro" ingredient substitutes such as lipids, carbohydrates, and proteins; enzymes used in food processing; fiber sources; complex mixtures; herbals in conventional foods; and ingredients new to infant formulas. For such substances, FDA reviewers must move beyond the framework of toxicological study review, in much the same way they did for the review of the direct additive olestra. For example, there may be situations where frank toxicity is simply not observed, no matter how high the dose or the duration of the study. In such cases, reviewers rely more on absorption, distribution, metabolism, and excretion studies, or even on chemical identity and structure-activity relationships. In these cases, human "tolerance" and clinical studies play a greater role. Further, after decisions are made and a product is on the market, postmarket monitoring and compilation of both passive and active adverse response reports may yield important information to confirm the original safety decision in light of actual use by many people.

Examples of substances for which the agency has received GRAS notices are such single chemical entities as the carbohydrates erythritol, arabinogalactan, gamma cyclodextrin, trehalose, and fructoligosaccharide. These are, as a broad class, intrinsically not very toxic, i.e., they have relatively "innocuous" chemical structures and often do not elicit frank toxicities in feeding studies. Traditional toxicology studies on such substances are thus less useful in reaching safety conclusions. Rather, for such substances, human "tolerance" studies sometimes take on added importance. Furthermore, these types of compounds often have rather large existing knowledge bases from which to draw conclusions about *general recognition* of safety by qualified members of the scientific community.

An example of a GRAS notice, FDA recently reviewed mycoprotein. Mycoprotein is a food ingredient of fungal origin (*fusarium venenatum*) that, because of its meat-like texture, is used as a meat substitute in processed prepared foods. A GRAS notice was submitted to the FDA for a use of this material in January 2001. Interestingly, FDA is also currently reviewing a food additive petition for this material as well. Major components of mycoprotein are, of course, protein, as well as fiber and lipids. The product has been on the market in Europe for over a decade.

Recently, FDA was made aware of reports of vomiting in certain individuals consuming foods with this new ingredient.

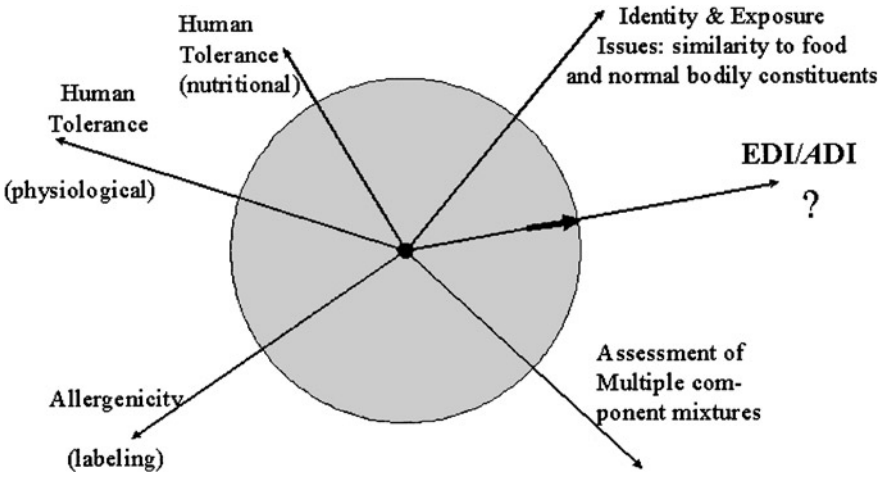

FIGURE 3

The circle of reasonable certainty of no harm with multiple dimensions. For many situations today, there may be multiple considerations beyond the simple ratio of EDI/ADI that must be evaluated in the course of reaching safety judgments.

FDA is currently following up on these reports to ascertain whether they have importance in the overall safety evaluation, i.e., whether they amount to "*harm to health*" for the purposes of the statutory safety standard.

As a result of broadening its approach to safety assessment of food ingredients by focusing on a wider range of parameters than only the EDI and the corresponding ADI, the safety judgment itself necessarily becomes broader in scope. Today, the simple "circle of reasonable certainty of no harm" has become multidimensional (Figure 3). This causes one to focus on not only EDI/ADI comparisons for an additive, but also on chemical identity and the similarity to normal bodily constituents, on human tolerance and clinical studies that provide data on nutritional and physiological effects, on information about allergenicity (with the necessary consequences for labeling), on nontraditional toxicological feeding studies and even in some cases on the need to focus on complicated multicomponent mixtures of substances and their associated toxicities and effect profiles.

On top of all this are the new "omic" technologies. Toxicogenomics, for example, has the potential to provide the agency with a deluge of detailed information about the potential relationship between phenotypic manifestations of the genotypic effects of a compound. In kind, the emerging fields of proteomics and metabonomics will further enrich the database with which the FDA reviewer must grapple. It is not clear yet how the agency will go about making use of such data to evaluate safety. Nevertheless, the challenge ahead is to keep expanding the process of safety evaluation to an ever-broader collection of possible food ingredients while at the same time opening the process of safety evaluation to include more and different tools by which to evaluate safety. All this must occur, of course, while ensuring that the original intent and purpose of the statute is preserved to protect public health through safety assessment.

CUMULATIVE RISK ASSESSMENT OF PESTICIDES SHARING A COMMON MECHANISM OF TOXICITY (Vicki L. Dellarco)

In assessing the potential health risks associated with exposure to pesticides, attention has historically focused on single pathways of exposure, e.g., from pesticide residues in food, water, or nonoccupational uses, for individual chemicals. Cumulative risk assessment and research on chemical mixtures, however, have taken on increased importance at the United States Environmental Protection Agency (EPA). This was underscored by the 1996 *Food Quality Protection Act* (FQPA) that directed the EPA, among other things, to take into account, when setting pesticide tolerances (maximum residues legally allowed on a food), available evidence concerning the cumulative effects of pesticides that have a common mechanism of toxicity, and to consider aggregate dietary and nonoccupational pathways of exposure. In light of FQPA, assessment of cumulative risk, although complex, is a high priority of the EPA. FQPA requires the EPA to place the highest priority for tolerance reassessment on agricultural pesticides that appear to pose the greatest risk, such as the organophosphorus (OP) pesticides. In December 2001, the EPA issued its "Preliminary OP Cumulative Risk Assessment" for comment, and in June 2002 published its revised cumulative risk assessment for the OP pesticides.[3] The cumulative risk assessment of OP pesticides provides a new way of analyzing data and represents the first probabilistic assessment of multichemical and multipathway exposures to pesticides.

To implement the cumulative provision of FQPA, the EPA has been working over the last several years to develop guidance and methodologies for conducting cumulative risk assessments, and then conduct its first such risk assessment on the

[3]www.epa.gov/pesticides/cumulative/rra_op/

OP pesticides. The EPA recently published guidance for evaluating and estimating the potential human risks associated with multichemical and multipathway exposures for common mechanism pesticides.[4] This guidance discusses the key principles that should be considered, and presents an analytical framework that describes the cumulative risk process in a series of steps. Using the OP cumulative analysis, the hazard and dose-response components of the guidance will be highlighted with some remarks on risk calculation methods. The exposure component of the cumulative risk process will not be included but is discussed in the guidance documents.

For common mechanism chemicals to pose a cumulative risk, they must have an opportunity to operate by that common mechanism of toxicity and have their effects or their exposures overlap. The essence of the cumulative assessment process is to estimate co-occurrences in exposure to multiple chemicals and the likely combined effect of those from different exposure pathways, i.e., food, drinking water, and nonoccupational. The determination of co-occurrences is based on scenarios that reflect the spatial, temporal, and demographic linkages to the common toxic effect that would be maintained for each hypothetical individual in the assessment. Thus, a cumulative risk assessment is multidimensional that considers who is exposed, to which chemicals and in what amounts and for how long, and will the exposures to an individual occur in the same location such that they will be experienced together.

The cumulative risk assessment begins with the identification of a group of chemicals that induce a common toxic effect by a common mechanism of toxicity. A separate guidance document was published for identifying common mechanism chemicals.[5] For the OP pesticides, this determination was made and peer reviewed in 1998. The OP pesticides were grouped on their shared ability to target and inhibit the enzyme acetylcholinesterase. The inhibition of acetylcholinesterase leads to accumulation of acetylcholine in the synaptic junction, leading to overstimulation of postsynaptic cholinergic receptors and consequent signs of neurotoxicity.

The next step in the process was to select an appropriate method and data set for combining the risks from exposures to several pesticides from more than one source and route. Although a group of chemicals may produce a common effect by a common mechanism of toxicity, they will have different toxic potencies for producing that effect. Thus, the chemical potency of each compound needs to be put on a common scale so their exposures can be normalized and combined. The cumulative guidance recommends use of dose addition for determining cumulative risk, which is consistent with the EPA's approach to multichemical assessments that involve common mechanism chemicals. For the OP pesticides, the relative potency factor (RPF) was used.

Briefly, the RPF uses an index chemical as the point of reference for standardizing the common toxicity of the chemical members. RPFs, i.e., the ratio of the toxic potency of a given chemical to that of the index chemical, are then used to convert exposures of all chemical members into exposure equivalents of the index chemical. The RPF approach utilizes an estimate of each OP's potency for the common toxicity, and allows for the quantification of exposure as it relates to the joint risk of the chemical group. Although a biological or pharmacokinetic modeling approach would have advantages in determining the cumulative risk for these OPs, the input parameters for such an approach are not available. Therefore, simple dose addition was applied and an empirical curve fitting model, i.e., the exponential model described below, was used to determine the RPFs.

The determination of toxic potency should, to the extent feasible with available data, be conducted on a uniform basis, i.e., same measure of potency, for the same effect, from the same test species/sex using studies of comparable methodology. A large body of data describing the inhibition of acetylcholinesterase in different species (rat, dog, mouse, rabbits) and for different tissues (plasma, red blood cells, and brain) has been generated for each OP. During the hazard analysis phase for the OP pesticides, studies using the rat provided the most extensive database for the various cholinesterase measures, and provided the best uniform basis for determining relative potency factors. Because human exposure to OPs can be through a number of different routes, namely the diet (both food and water) and nonoccupational exposures at home, school, and office buildings, it was necessary to review and analyze the cholinesterase data for the oral, dermal, and inhalation routes of exposure. After the plasma, red blood cell (RBC) and brain cholinestrease data were analyzed, brain acetylcholinesterase data from female rats was selected as the basis for developing RPFs for use in the assessment for several reasons. Female data were selected because it was the most sensitive sex for several OP pesticides compared to responses in the male rat. Brain acetylcholinesterase inhibition is an appropriate end point for use as an adverse effect because it reflects a response in a target tissue of concern that is relevant to humans. Brain acetylcholinesterase inhibition is an acknowledged adverse effect in both humans and in laboratory animals. Therefore, error due to the extrapolation between the response in a surrogate tissue, i.e., RBC and plasma, and a target tissue itself (brain) is eliminated. In addition, the data for the brain compartment have very tight confidence limits when compared to those from the plasma and RBC compartments, suggesting that there is much less variability in this compartment across the database.

In order to provide a stable and uniform basis for determining the relative toxic potency of these OP pesticides, steady-state cholinesterase data were selected for further analysis, i.e., the point at which little or no change occurs in the degree of inhibition resulting from continued administration of the dose for a longer period. Examination of the rat data suggested that cholinesterase inhibition reached steady-state approximately

[4] www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf

[5] www.epa.gov/fedrgstr/EPA_PEST/1999/February/Day_05/6055.pdf

21 to 30 days after the start of dosing for OP pesticides. Thus, studies of 21 days or longer were used for calculations of RPFs. The choice of using steady-state cholinesterase data was also made because the likelihood of encountering an exposure to OPs with no prior recent exposure was considered to be very small. Also, the agricultural uses of OPs are limited and the resulting residues that occur in food and water, as well as exposure due to the application of OPs in homes across the United States are expected to be small. In addition, following exposure to an OP, regeneration of cholinesterase to preexposure levels occurs in the time scale of days to weeks, not a single day, making the exposed individual potentially more vulnerable to subsequent exposures during that period.

There are several methods that can be used to compare toxic potency among chemicals, including the use of NOAELs and the use of benchmark dose (BMD) modeling approach. Rather than basing the determination of toxic potency on NOAELs, which are a function of study design, the oral cholinesterase data were fitted to a mathematical function that permitted consideration of the entire dose-response curve for each OP pesticide. EPA's Office of Research and Development developed a dose-response modeling approach that permitted the combining of many studies and cholinesterase data sets, calculation of confidence limits, and estimation of each OP's toxic potency. A nonlinear exponential model was used, which provided a good fit of the cholinesterase data as determined by goodness-of-fit tests. A more complex model could not be used because the size of the data sets constrained the number of parameters. A joint analysis was done for each pesticide using multiple studies and multiple time measurements of cholinesterase activity. The joint analysis permitted the shape of each OP dose-response curve to be shared among different data sets, allowed low-dose issues to be explored, and generated more robust estimates of toxic potency. It also accounted for study to study variability.

As mentioned above, dose additivity was assumed by application of a single model to all of the OP dose-response curves. In the OP assessment, there is some uncertainty surrounding the assumption of dose additivity given that the ß values (horizontal asymptotes) are heterogeneous among the OPs analyzed. This heterogeneity is indicative that the dose-response curves are not parallel and, therefore, the application of simple dose addition is only an approximation of combined risk. Dose additivity assumes that the common mechanism chemicals behave in a similar fashion, have similar pharmacokinetic and pharmacodynamics characteristics, and that their dose-response curves will be parallel, i.e., the ratios of their relative toxic potencies remain the same throughout their dose range. The underlying biological processes that determine the toxic potency of each OP are extremely complex and involve several metabolic systems as well as resynthesis rates of the different cholinesterases. The activation and/or deactivation rates differ for some of these pesticides. The current information on OP mixture interactions and pharmacokinetics/pharmacodynamics does not provide a sufficient basis to depart from the assumption of dose additivity.

To address the uncertainty in extrapolating to lower human exposures, a low-dose model estimate (BMD_{10}) was used to calculate OP RPFs. The BMD_{10} is the point at which cholinesterase inhibition can be reliably shown to have changed by 10% due to dosing. Various degrees of rat brain cholinesterase inhibition was analyzed (1% to 20%) and 10% brain cholinesterase inhibition was indeed found to be at the low end of detection.

Although the cholinesterase data used for the oral route of exposure was quite extensive for dose-response modeling for the OP pesticides, the data for the inhalation and dermal routes tended to be less extensive and not as robust for dose-response modeling. Thus, comparable-effect dose levels (a dose at which a maximum of 10% to 15% cholinesterase inhibition was reported) were selected as the basis for determining relative toxic potencies.

In order to reduce uncertainty in the cumulative risk assessment, consideration of high-quality dose-response data for the common toxic effect is very important in selecting an index chemical. The role of the index chemical in the cumulative risk assessment process is twofold. First, it serves as a basis for calculating the RPFs. Thus, the potency of every chemical in the group will be compared to the index chemical. Second, the point of departure (POD) for the index chemical will be used to extrapolate and estimate cumulative risk estimations. In order to do a comprehensive search for the best index chemical, all OPs were initially considered as potential candidates. Sequentially, the index chemical was selected following the dose-response analysis of the oral data set and review of the dermal and inhalation toxicity studies. Methamidophos was selected as the index chemical. Methamidophos has sufficient data for cholinesterase inhibition to support modeling of a BMD_{10} by all three routes of exposure. Given that the RPF method portrays risk at exposure equivalents to one chemical (the index compound), it is preferred that the index chemical have a high-quality database. Dose-response data for methamidophos permits reliable estimates of PODs for all routes without resorting to the use of the less precise NOAELs. Certainty of the PODs was considered to be of great importance because they will impact the outcome of the assessment to a greater extent than any other aspect of the toxicity database. The oral relative potency factors for the OPs are depicted in Figure 4. Their toxic potencies span about 5 orders of magnitude and their order of potency matches nicely with what we know about the toxicity of the individual pesticides.

The last key step in the dose-response analysis is to determine an extrapolation point or point of departure for the chemicals in the cumulative assessment group. A POD was derived from the dose-response curve of the index chemical, which was used to determine cumulative risk. The PODs for methamidophos for all three routes were calculated with dose-response modeling using the exponential equation. A BMD_{10} was selected for the POD, given that this level of cholinesterase inhibition was at the limit of detection. The PODs used in the OP cumulative risk assessment were for female brain cholinesterase inhibition

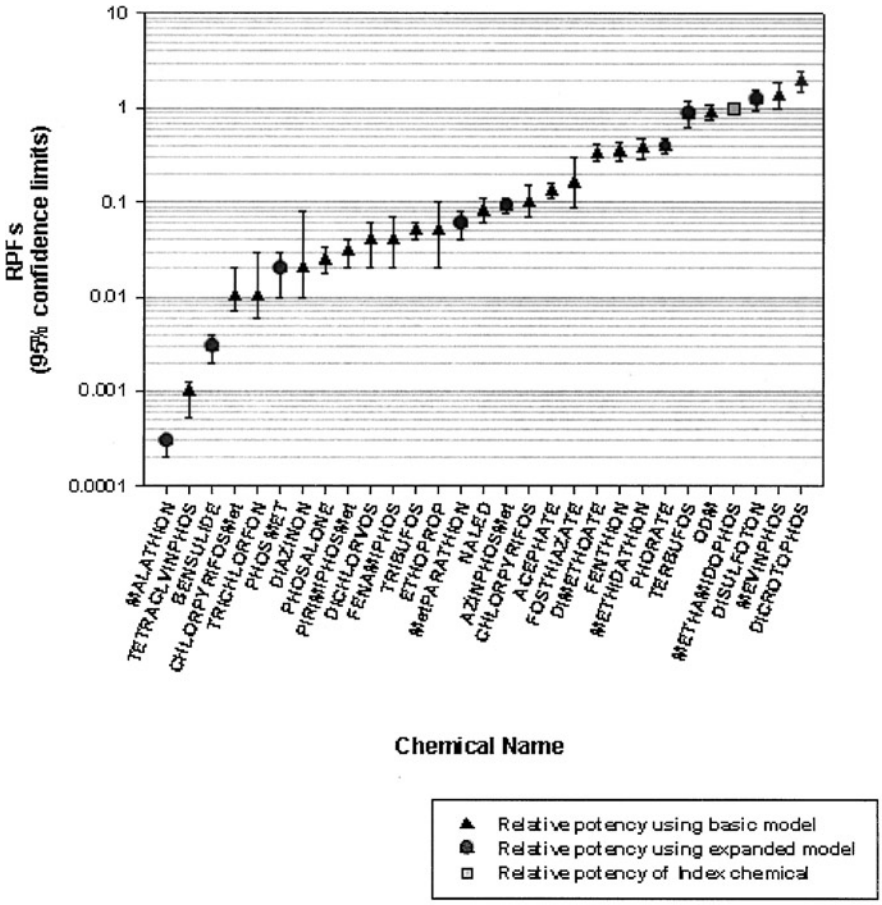

FIGURE 4
Relative potency factors for organophosphorous compounds and brain cholinesterase inhibition (ChEI).

(oral = 0.08 mg/kg/day; dermal = 2.12 mg/kg/day; inhalation = 0.39 mg/kg/day).

The cumulative risks for the OPs were expressed as the total pesticide residues for the chemical members in terms of the Index Chemical. The POD for methamidophos was used to calculate route-specific margin of exposures (MOEs):

$$\mathrm{MOE} = \mathrm{POD}_{\mathrm{Index}} \div \sum_{Route} \mathrm{Exposure}$$

MOEs are combined by taking the inverse of the different pathway MOE and then taking the inverse of that sum. This MOE approaches permits the route-specific nature of the risk estimates to be preserved. This MOE equation is then used to produce a distribution of daily estimates of cumulative exposures. In the OP cumulative assessment, Calendex was used to generate the distributions of resulting MOEs. This software program uses the concept of a 365-day calendar and probabilistic techniques to appropriately combine exposures from the food, drinking water and residential/nonoccupational pathways. It allows one to track potentially exposed individuals on a daily basis that preserves all appropriate linkages in a manner that incorporates probabilities of exposure, use and application practices, age and human activity patterns, and seasonality and timing of exposure. There are several different exposure models in different stages of development that can integrate various pathways while simultaneously incorporating the time dimensions of the data, including, Calendex, LifeLine, and Cumulative and Aggregate Risk Exposure Model (CARES). All three of these models provide comparable results for the OP pesticides, thus giving confidence that the results of the cumulative assessment were not model driven.

Although the exposure component was not covered in detail, it is noteworthy to point out that the revised cumulative risk assessment for OP pesticides is based upon comprehensive and data-specific exposure information for estimated exposures from food, drinking water, and nonoccupational uses. The data were treated in the analysis in large part in the form of distributions, permitting the assessment to reflect the full range of variability in each input parameter. The food pathway was assessed nationally, but because the United States is climatologically and geographically diverse, the United States was divided into Regions to account for factors such as weather and soil type (these affect the amounts and types of pesticides used)

in estimating exposure to drinking water and nonoccupational uses.

The last step of the assessment process is to characterize the risk. The results and conclusions of the cumulative risk analysis are clearly described in the guidance document, including the relative confidence in toxicity and exposure data sources and model inputs. The risk characterization also includes a description of the variability. Major areas of uncertainty are described both qualitatively and quantitatively. The magnitude and direction of likely bias and the impact on the final assessment are also discussed. Risk contributors were identified with regard to pesticide(s), pathway, source, time of year, and impacted subpopulations (with attention to children). It is important to consider the range of risk assessment values generated for a cumulative risk assessment, which in turn takes into account different exposure periods for different age groups, living in different regions, with risks shown at different percentiles of estimated exposures in the population.

Based on the estimated margin of exposures, most uses of OP pesticides on food crops do not significantly contribute to the cumulative risk. Only a few chemical/crop combinations were found to play a role in the food assessment and it appeared that one of the major factors influencing the results for certain individual OP's involved chemicals where risk assessments and mitigation actions have not been finalized. EPA found that drinking water is not a significant source of exposure after evaluating the contribution to overall exposure resulting from OP residues across different regions of the country, including the impacts from periods of high-volume runoff, e.g., during the spring and storm events. Many residential uses of OP pesticides have been cancelled; residential uses have been reduced by >20 million pounds annually. Thus, it was not surprising to find that residential uses are not a significant contributor to the OP cumulative risk. The only residential use that plays a role in the risk estimates is the indoor use of dichlorvos on pest strips.

In summary, after several years of scientific work, countless scientific reviews and public meetings, and risk mitigation efforts on the part of the regulated community, the cumulative risk assessment of OP pesticide food safety contains good news for US consumers.

COMPARING US EPA OFFICE OF PESTICIDE PROGRAMS AND WORLD HEALTH ORGANIZATION ACCEPTABLE DAILY INTAKES FOR PESTICIDES (George M. Gray)

Many organizations around the world establish standards for pesticide exposure. Called by various names including reference doses, acceptable daily intakes, or tolerable intakes, these standards are intended to set a level of pesticide residues on food products that will pose a negligible risk to consumers.

In most cases, tools of risk assessment are used to establish these levels. Epidemiologic and toxicological data are evaluated to determine a "critical effect" that is used in dose-response evaluation. In most cases, the NOAEL for the critical effect is adjusted by factors, varyingly called safety factors or uncertainty factors or adjustment factors, to establish an acceptable level of exposure. In some instances, probabilistic methods are used if the compound has shown carcinogenic potential in animal tests. A de minimus level of risk is then used in setting specific pesticide and crop tolerances. ADI levels are used in risk management by comparing estimates of intake based on the different crops on which the pesticides are used and the consumption patterns of foods derived from those crops to the acceptable level of exposure.

In this study, ADIs for the same pesticides established by the US EPA and the WHO are compared through construction of the ratio of the EPA ADI to the WHO ADI. Both US EPA and WHO focus on noncancer effects when setting ADIs (W. Burnam, US EPA Office of Pesticide Programs [OPP], personal communication, 2003) and use similar approaches. If a compound is a suspected carcinogen, the US EPA also calculates a cancer slope factor (EPA 1986) for use in risk management. The WHO specifically rules out the use of probabilistic methods for risk assessment of carcinogens (IPSC 1990). To investigate whether the two groups might assess the noncancer risks of carcinogenic compounds differently, the ratios were examined separately for potential carcinogens and noncarcinogens. Finally, possible reasons for differences in stringency between US EPA and WHO are discussed, as are the implications of our findings for discussions about the role of precaution in risk assessment and risk management.

EPA and WHO ADI values were taken from the 1997 *US EPA Reference Dose Tracking Report* (EPA 1997). A selection of the WHO values was checked against the International Program on Chemical Safety Inventory of International Program on Chemical Safety (IPCS) and WHO Pesticide Evaluations through 2001 (IPCS 2003). Only compounds with both EPA and WHO ADIs were compared. Banned pesticides were removed. There were a total of 111 pesticides in the analysis (Table 2).

The ADIs were compared by constructing the ratio of the US EPA ADI to the WHO ADI. The distribution of ratios was then plotted and evaluated (Figure 5). The distribution clearly shows a much larger proportion of ratios smaller than one (EPA value more stringent). The geometric mean of the ratios is 0.44.

Also plotted are the distributions for pesticides designated as category B (probable human carcinogen) or C (possible human carcinogen—quantify) by the US EPA (Figure 6) and those considered noncarcinogens (Figure 7). The geometric mean for the potential carcinogens and noncarcinogens is 0.41 and 0.46, respectively. Although there is not a significant difference in the geometric means for the two distributions, it can be seen that for carcinogens, only 6 out of 38 (16%) of WHO values are lower than the EPA values, whereas for noncarcinogens, 20 out of 74 (27%) have more stringent WHO values.

There are a large number of compounds with the same ADI from both organizations but it is clear that, on average, the EPA OPP generally sets lower ADIs than does the WHO. It is likely

TABLE 2
EPA and WHO acceptable daily intake values for pesticides

Name	CASRN	OPP ADI (mg/kg/day)	WHO ADI (mg/kg/day)
2,4-D (acid + salts)	94-75-7	0.0100	0.3000
Acephate	30560-19-1	0.0040	0.0300
Aldicarb (Tern ik)	116-06-3	0.0010	0.0030
Anilazine (Dyrene)	101-05-3	0.0004	0.1000
Avermectin B1	65195-55-3	0.0004	0.0001
Azinphos—methyl (Guthion)	86-50-0	0.0015	0.0050
Baycor (Bitertanol)	55179-31-2	0.0063	0.0100
Baygon (Propoxur)	114-26-1	0.0050	0.0200
Bendiocarb	22781-23-3	0.0050	0.0040
Bentazon (Basagran)	25057-89-0	0.0300	0.1000
Biferthrin (Talstar)	82657-04-3	0.0150	0.0200
Bromorn ethane	74-83-9	0.0014	1.0000
Captan	133-06-2	0.1300	0.1000
Carbaryl	63-25-2	0.0140	0.0100
Carbofuran	1563-66-2	0.0050	0.0100
Carbophenothion	786-19-6	0.0001	0.0005
Carbosulfan (FMC 35001)	55285-14-8	0.0100	0.0100
Chlorobenzilate	510-15-6	0.0200	0.0200
Chlorothalonil	1897-45-6	0.0200	0.0300
Chlorpyrifos	2921-88-2	0.0030	0.0100
Chlorpyrifos—methyl	5598-13-0	0.0100	0.0100
Clofentezine (Apollo)	74115-24-5	0.0130	0.0200
Cyfluthrin (Baythroid)	68359-37-5	0.0250	0.0200
Cyhalothrin/Karate	68085-85-8	0.0010	0.0200
Cyhexatin (TCTH)	13121-70-5	0.0008	0.0010
Cypermethrin (Ammo)	52315-07-8	0.0100	0.0500
Cyrom azine (Larvadex)	66215-27-8	0.0075	0.0200
Deltamethrin (Deca-)	52918-63-5	0.0100	0.0100
Diazinon	333-41-5	0.0001	0.0020
Dichlorvos (DDVP)	62-73-7	0.0050	0.0040
Dicloran (DCNA/Botran)	99-30-9	0.0250	0.0300
Dicofol (Kelthane)	115-32-2	0.0012	0.0020
Difubenzuron (Dimilin)	35367-38-5	0.0200	0.0200
Dimethipin (Harvade)	55290-64-7	0.0200	0.0200
Dimethoate	60-51-5	0.0005	0.0100
Dinocap (Karathane)	39300-45-3	0.0040	0.0010
Diphenylamine	122-39-4	0.0300	0.0200
Diquat dibromide	85-00-7	0.0050	0.0020
Disulfoton	298-04-4	0.0003	0.0003
Dodine acetate		0.0040	0.0100
Ebufos (Icadusafos/Apache)	95465-99-9	0.0000	0.0000
Endosulfan	115-29-7	0.0060	0.0060
Ephephon	16672-87-0	0.0180	0.0500
Ethion	563-12-2	0.0005	0.0020
Ethofenprox (Etofenprox)	80844-07-1	0.0500	0.0300
Ethoprop (Ethoprophos)	13194-48-4	0.0001	0.0003
Ethoxyquin	91-53-2	0.0300	0.0600
Ethylene thiourea (ETU)	96-45-7	0.0001	0.0040

(Continued on next page)

TABLE 2
EPA and WHO acceptable daily intake values for pesticides *(Continued)*

Name	CASRN	OPP ADI (mg/kg/day)	WHO ADI (mg/kg/day)
Fenamiphos (Nemacur)	22224-92-6	0.0001	0.0005
Fenbutatin oxide (Vendex)	13356-08-6	0.0500	0.0300
Fenitrothion (Sumithion)	122-14-5	0.0013	0.0050
Fenpropathrin (Danitol)	39515-41-8	0.0250	0.0300
Fensulfothion	115-90-2	0.0003	0.0003
Fenthion	55-38-9	0.0007	0.0010
Fenvalerate (Pydrin)	51630-58-1	0.0250	0.0200
Flusilazole (Nustar)	85509-19-9	0.0007	0.0010
Folpet	133-07-3	0.0090	0.0100
Glufosinate—ammonium	77182-82-2	0.0200	0.0200
Glyphosate (+ salts)	1071-83-6	2.0000	1.7500
Hexaconazole (Anvil)	79983-71-4	0.0200	0.0050
Hexythiazox (Savey)	78587-05-0	0.0250	0.0300
Imazalil	35554-44-0	0.0250	0.0300
Iprodione (Glycophene)	36734-19-7	0.0600	0.2000
Isofenphos (Amaze)	25311-71-1	0.0005	0.0010
Lindane (gamma BHC)	58-89-9	0.0047	0.0080
Malathion	121-75-5	0.0200	0.0200
Maleic hydrazide	123-33-1	0.2500	0.5000
Mancozeb		0.0030	0.0300
Maneb	12427-28-2	0.0050	0.0500
Metalazyl	57837-19-1	0.0740	0.0300
Methamidophos (Monitor)	10265-92-6	0.0010	0.0040
Methidathion	950-37-8	0.0015	0.0010
Methiocarb (Mesurol)	2032-65-7	0.0050	0.0010
Methomyl	16752-77-5	0.0080	0.0300
Methoxychlor	72-43-5	0.0050	0.1000
Methyl parathion	298-00-0	0.0003	0.0200
Metiram	9006-42-2	0.0003	0.0300
Mevinphos (Phosdrin)	7786-34-7	0.0003	0.0015
Monocrotophos (Azodrin)	6923-22-4	0.0001	0.0006
Myclobutanil (Systane/Rally)	88671-89-0	0.0250	0.0300
Oxamyl (Vydate)	23135-22-0	0.0002	0.0300
Oxydemeton—methyl	301-12-2	0.0005	0.0003
Oxythioquinox (Morestan)		0.0060	0.0060
Paclobutrazol	76738-62-0	0.0250	0.0100
Paraquat dichloride	1910-42-5	0.0045	0.0040
Parathion (ethyl parathion)	56-38-2	0.0003	0.0050
Pentachloronitrobenzene	82-68-8	0.0030	0.0070
Permethrin	52645-53-1	0.0500	0.0500
Phorate (Thimet)	298-02-2	0.0005	0.0002
Phosalone	2310-17-0	0.0025	0.0010
Phosmet (Imidan)	732-11-6	0.0100	0.0200
Phosphamidon	13171-21-6	0.0002	0.0005
Piperonyl butoxide	51-03-6	0.0175	0.0300
Pirimiphos—methyl	29232-93-7	0.0100	0.0300
Prochloraz	67747-09-5	0.0075	0.0100
Procymidone (Sumilex)	32809-16-8	0.0350	0.1000

(Continued)

TABLE 2
EPA and WHO acceptable daily intake values for pesticides *(Continued)*

Name	CASRN	OPP ADI (mg/kg/day)	WHO ADI (mg/kg/day)
Profenofos (Curacron)	41198-08-7	0.0001	0.0100
Propargite (Omite)	2312-35-8	0.0400	0.1500
Propiconazole (Banner/Tilt)	60207-90-1	0.0130	0.0400
Pyrethrins	121-21-1	0.0640	0.0400
Sumithrin (Phenothrin)	26002-80-2	0.0710	0.0700
Terbufos	13071-79-9	0.0001	0.0002
Thiabendazole (+ salt)	148-79-8	0.1000	0.1000
Thiodicarb (Larvin)	59669-26-0	0.0300	0.0300
Thiophanate—methyl	23564-05-8	0.0800	0.0800
Thiram	137-26-8	0.0080	0.0100
Triadimenfon (Bayleton)	43121-43-3	0.0400	0.0300
Triadimenol (Baytan)	55219-65-3	0.0380	0.0500
Triforine (Funginex)	26644-46-2	0.0250	0.0200
Triphenyltin hydroxide	76-87-9	0.0003	0.0005
Vindozolin (ronilan)	50471-44-8	0.0120	0.0700

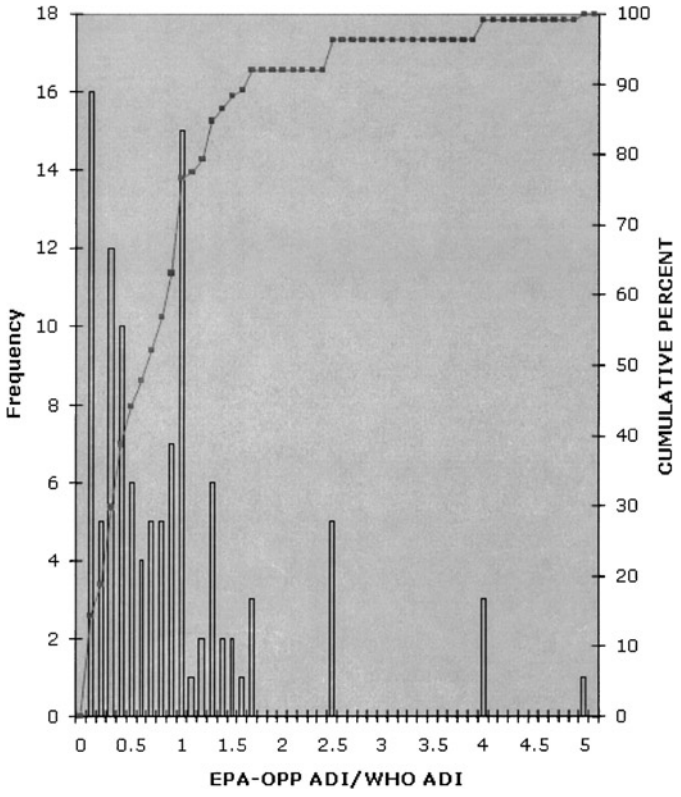

FIGURE 5
Frequency (*bar*) and cumulative percent (*line*) of the EPA/WHO ADIs for 111 pesticides.

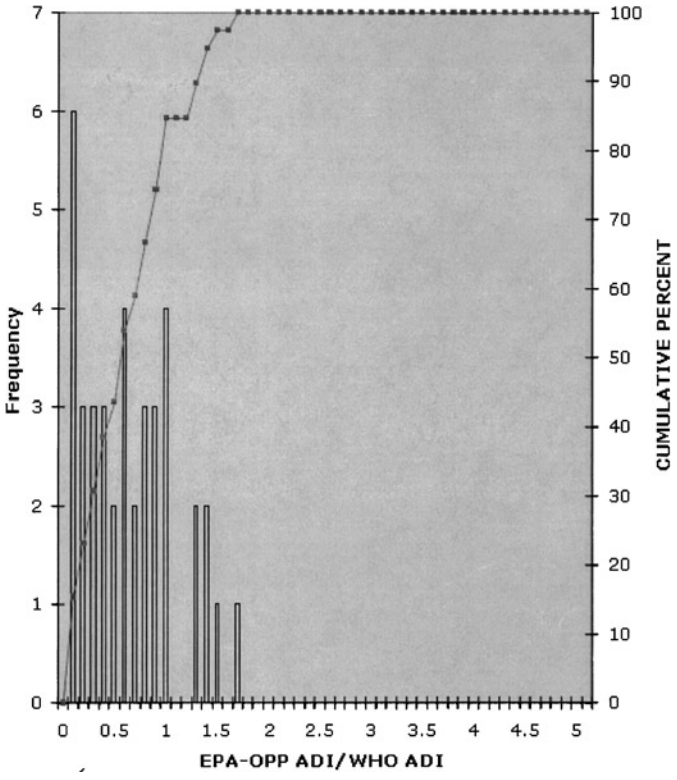

FIGURE 6
Frequency (*bar*) and cumulative percent (*line*) of US EPA/WHO ADIs for 38 carcinogenic pesticides.

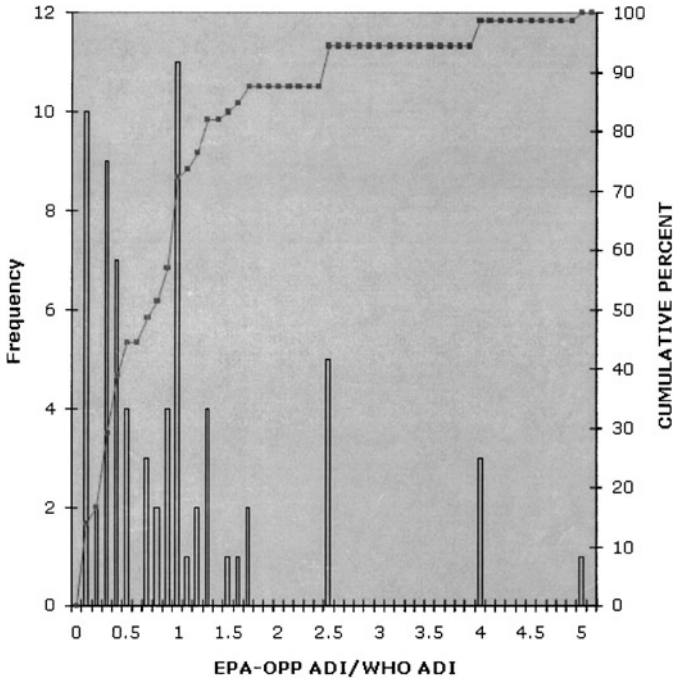

FIGURE 7
Frequency (*bar*) and cumulative percent (*line*) of US EPA/WHO ADIs for 74 noncarcinogenic pesticides.

that differences in risk assessment approaches play some role in this difference.

This finding is surprising in that both EPA and WHO are using the same "safety factor" or "uncertainty factor" approach to noncancer risk assessment in establishing ADIs (Barnes and Dourson 1988). There are, however, additional key choices and assumptions in the risk assessment process that could explain systematically more stringent assessments from US EPA. Perhaps the most likely explanation for differences in WHO and EPA ADI levels, related to choices in the risk assessment process, is the severity of end points chosen as the "critical effect" in evaluating the toxicological database for a chemical. It may be that the EPA focuses on more subtle end points whereas the WHO process chooses toxicological effects with more direct correlation with clinical effects that occur at higher levels of exposure. These sorts of judgments are rarely dictated by formal procedures or guidelines but are more often part of the "culture" of a particular organization and, for this reason, may be less obvious.

Although neither group uses potential cancer findings in setting ADIs, it is conceivable that knowledge of potential carcinogenicity might influence setting of the ADI. Although the geometric mean of the ADI ratios for carcinogens is similar to that for noncarcinogens (0.41 versus 0.46), the distributions do suggest that the US EPA may be more stringent in setting ADIs (nominally based on noncancer effects) of a compound that is a suspected carcinogen.

A potential shortcoming of this analysis is the lack of control on timing for setting of the ADI. It is possible that the timing of pesticide review and setting of the ADI or revision could differ significantly between organizations. If new data and information become available, there could be valid scientific reasons for the different ADIs. However, there seems to be little reason to expect that either EPA or WHO had significantly more new (or old) values.

This preliminary analysis does identify several risk assessment issues that are likely to extend to other arenas of risk management. First, are different "safe" levels for the same compounds due to differences in risk assessment methods not differences in data? If it is indeed due to different risk assessment techniques and choices, then it raises interesting questions for harmonization of risk management across jurisdictions. The second issue is related to the debate around the precautionary principle (Lofstedt 2002). The US government has argued for several years that American approaches to risk management does embody precaution and that it is exercised to a great extent in risk assessment approaches (Graham 2002). This analysis would seem to support this idea by suggesting that if precaution is equivalent to regulatory stringency, the US is indeed more precautionary in setting ADIs for pesticides in foods.

DISCUSSION AND CONCLUSIONS

The papers presented in this symposium provide an excellent perspective on the range of differences used in the assessment of risks posed by food constituents and ingredients. The differences occur within agencies, between agencies, between countries, within international organizations, and over time. We are left with a bewildering array of methodologies and outcomes. Does this help anyone, from toxicologists to the ordinary consumer of foods, be better informed? Can we compare the risks from dioxins in meat to the methyl mercury in fish and decide where to place resources or what to have for dinner?

At one time, it was perhaps possible to think most of the differences in risk assessment methodologies as "anomalies." That is, although there were many methods being used, one method would evolve and supercede the others. In time, the risk assessor would be left with one preferred method of assessing risks that would give us a "true" picture of risk. Both professionals and the public would be able to "understand" a risk number developed and use it to make informed decisions.

For better or worse, the differences in risk assessment methodologies will be with us for the foreseeable future. This is because laws are written that force a certain approach to risk assessment that tie the hands of an agency to do what might even be termed "poor" risk assessments. Public pressure and perceptions force certain approaches as well. Finally, all organizations are subject to internal inertia and will not change unless forced to.

The question used to be, "How can we harmonize our risk assessments?" Now it is, "How do we avoid making the differences so large that it impairs trade, confuses everyone, and frightens the public?" The papers presented at this symposium give us clues about where we can put our resources to mitigate such discrepancies. Dr. Rodricks' idea of developing a scheme

to evaluate the benefits and risks of foods and food ingredients seems to be a logical place to start. We need a process that does not look at risks in a vacuum. The benefits of certain fatty acids in fish may outweigh the adverse effects of methyl mercury. A process that weighs all the risks and benefits of food constituents, whole foods, and diets, is desperately needed.

Dr. Rulis' description of the work FDA has been doing with the data at its disposal is very encouraging. A thorough, systematic evaluation of all the toxicology and clinical data already in existence can show us where safety lies and where the risks may be. That knowledge allows risk assessment methods to be developed that focus on the difficult areas. They can then be used to protect the public health without affecting progress, trade or sanity. Further, over time, it will allow the development of refined safety factors that will ensure public health.

Dr. Dellarco's example of the amount of work needed to fulfill a legislative requirement provides a number of lessons. The one that may be most important is that, despite the huge amount of work involved, risk assessments of mixtures or multiple contaminants can be done in a way that seems to make sense. This fits with Rodricks' proposition. The result poses a daunting challenge to develop the data and applications for the thousands of chemicals consumed in the course of a normal diet. Nonetheless, it can be done in a way that does not fly in the face of reason. This is very reassuring.

Dr. Gray's paper points out the problems with different approaches to risk assessment. While a lot of evaluations result in a similar risk values, a number do not. Furthermore, some values are amazingly different. These need to be reviewed and harmonized to the extent possible. Otherwise, consumers end up confused, and professionals look anything but, well, professional. Competing risks is not a way forward.

Using the thinking demonstrated at this symposium, the toxicology and risk assessment community should be able to start moving forward to develop a paradigm for assessing risk and benefit that maximizes public health. The academic sector may need to take this on first. Once established, regulatory officials and politicians will have a model to use in constructing regulations and laws. Then, changes can be made in operating procedures that will allow a unified, understandable, and realistic approach to assessing risks of foods. As stated in *The X Files*, the truth is out there . . .

REFERENCES

Barnes, D. G., and M. Dourson. 1988. Reference Dose (RfD): Description and use in health risk assessments. *Reg. Toxicol. Pharmacol.* 8:471–486.

Burnam, W. 2003. US EPA Office of Pesticide Programs, personal communication, April, 2003.

Environmental Protection Agency (EPA). 1986. *Guidelines for carcinogen risk assessment.* US Environmental Protection Agency: 51 FR33994–33997

EPA. 1997. Office of Pesticide Programs Reference Dose Tracking Report. United States General Accounting Office (USGAO). 1997. *Food safety: Fundamental changes needed to improve food safety*. Report 97-249. Washington, DC.

Federal Register. 1992. *Statement of policy: Foods derived from new plant varieties*. Notice, May 29, 1992. 57 FR 22984–23005.

Federal Register. 1993. *Toxicological principles for the safety of food additives* (The "Redbook"). U.S. Food and Drug Administration, March 29, 1993. 58 FR 16536 [http://vm.cfsan.fda.gov/~redbook/red-toca.html]

Federal Register. 1996. *Food additives permitted for direct addition to food for human consumption: Olestra, final rule*. January 30, 1996. 61 FR 3118–3173.

Federal Register. 1997. *Substances generally recognized as safe; proposed rule*. April 17, 1997. 62 FR 18938–18964.

Federal Register. 2001a. *Premarket notice concerning bioengineered foods; proposed rule*. January 18, 2001. 66 FR 4706–4738.

Federal Register. 2001b. *Draft guidance for industry: Voluntary labeling indicating whether foods have or have not been developed using bioengineering.* Available, January 18, 2001. 66 FR 4839–4842.

Francer, J. K., C. H. Jung, and S. S. Pak. 1998. *Food safety: Enhancing a fragmented regulatory system*. Cambridge, MA: John F. Kennedy School of Government. Harvard University.

Food Safety and Inspection Service (FSIS). 1997. *Hazard analysis and critical control point (HACCP) update*. June 17, 1997.

Gold, L. S., and E. Zeiger. 1997. *Handbook of Carcinogenic Potency and Genotoxicity Data Bases.* Boca Raton, FL: CRC Press.

Graham, J. D. 2002. The Role of Precaution in Risk Assessment and Management: An American's View. Remarks prepared by John Graham, Administrator of the Office of Information and Regulatory Affairs, U.S. Office of Management and Budget. January 11–12, 2002. Conference on The U.S., Europe, Precaution and Risk Management: A Comparative Case Study Analysis of the Management of Risk in a Complex World. [http://www.useu.be/RiskManagement/Jan1102GrahamUSRiskManagementPrecPrin.html]

Institute of Food Technologists (IFT). 1998. Guiding principles for optimum food safety oversight and regulation in the United States. *Food Technol.* 52:50–52.

International Program on Chemical Safety (IPCS). 1990. *Environmental Health Criteria 104, Principles for the toxicological assessment of pesticide residues in food.*

IPCS. 2003. *Inventory of IPCS and other WHO pesticide evaluations and summary of toxicological evaluations performed by the Joint Meeting on Pesticide Residues (JMPR) Evaluations through 2001*. http://www.inchem.org/documents/jmpr/jmpeval/jmpr2001.htm

Institute of Medicine (IOM). 1997–2001. *Dietary Reference Intakes*. Washington, DC: National Academy Press.

IOM. 1998. *Ensuring Safe Food: From Production to Consumption*. Washington, DC: National Academy Press.

Joint Food and Agriculture Organization of the United Nations/ World Health Organization (FAO/WHO) Expert Committee on Food Additives (JEFCA). 1965. Eighth Report. World Health Organization Technical Report Service. 309.

Lofstedt, R. 2002. The precautionary principle: Risk, regulation and politics. Presented at 21st Century Trust Conference on Precautionary Principle: Risk, Regulation and Politics. [http://www.21stcenturytrust.org/precprin.htm-]

Lofstedt, R. E., and D. Vogel. 2001. The changing character of regulations: A comparison of Europe and the United States. *Risk Anal*. 21:399–416.

National Academy of Sciences (NAS). 1983. *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC: National Academy Press.

NAS. 1994. *Science and Judgement in Risk Assessment,* Chapter 2. Washington, DC: National Academy Press.

Rodricks, J. V. 2000. Food constituents, additives, and contaminants. In *Environmental toxicants*, 2nd ed., ed. M. Lippman. New York: Wiley-Interscience.

Rulis, A. M. 1987. Safety assurance margins for food additives currently in use. *Reg. Toxicol. Pharmacol.* 7:160–168.

Woteki, C. E., and P. R. Thomas. 1992. *Eat for life*: *The Food and Nutrition Board's guide to reducing your risk of chronic disease*. Washington, DC: National Academy Press.