Food Safety: Revising the Statute

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Summary. There is increasing recognition that federal food safety laws and policies need to be revised. Congressional debate on proposed amendments to the Food, Drug, and Cosmetic Act has generated several different perspectives on how the food safety laws should be changed. Before a consensus can be reached, scientists, regulators, the food industry, and consumers will have to review such complex and controversial issues as the level of acceptable risk, the value of risk-benefit analysis, the proper role of independent scientific review, and the reliability of quantitative risk assessment.

Twenty-five years ago, when Congress last amended the food safety provisions of the federal Food, Drug, and Cosmetic Act (*1*), most experts believed that it was possible to eliminate from the food supply all substances that may increase the risk of cancer to humans or animals. The act as drafted by Congress required the Food and Drug Administration (FDA) to prohibit the use of substances that induce cancer in man or animals. Today, as Congress wrestles with new proposals to amend and update the statute, the goal of eliminating all such substances is viewed by many, including the FDA, as unattainable (*2*). Two developments have contributed to the change in perspective. First, because of improvements in analytical techniques minute quantities of carcinogenic constituents in food can be detected. These include environmental contaminants that enter the food chain, migrants from packaging materials, impurities in natural and synthetic additives, natural constituents of raw agricultural commodities, and residues of animal drugs found in food-producing animals. Second, contrary to the belief widely held in 1958, contemporary toxicological testing suggests that an array of nutrients may play some role in the carcinogenic process (*3*).

Although the gap between the existing statute and technological advances has been growing, the FDA has done a commendable job of ensuring the safety of our nation's food supply. However, the quality of the FDA's performance may not stem so much from the soundness of the act as from the way that the agency has interpreted the law, avoiding conclusions that a rigid reading of the law might yield (*4*).

An example was the agency's handling of selenium, a nutrient essential in low doses for normal growth and metabolism. It is added to animal feed since animals cannot produce it endogenously. Because in high doses selenium has produced tumors in test animals, the Delaney anticancer clauses of the Food, Drug, and Cosmetic Act might have required the FDA to ban it. To avoid this the agency adopted a novel and unproved theory, claiming that because it knew the mechanism by which selenium causes cancer in animals and because the substance acted as a secondary carcinogen, the Delaney anticancer clauses, which prohibit the use of any substance that induces cancer in animals or humans, did not apply (*5*). It is the inflexibility of current law that forces the FDA to stretch for such interpretations of the law, possibly sacrificing consistency and predictability to desired outcomes.

The regulatory dilemmas posed by both saccharin and nitrites also support the need for reform (*6*). Although both additives may have substantial health-related benefits—saccharin-sweetened products are used by millions of diabetics and weight-conscious consumers (*7*), and nitrites prevent botulism from growing in a wide variety of products—under current law the FDA could not consider the benefits in deciding how to regulate these substances.

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The inability of the FDA to deal realistically with these current problems will have profound consequences for all federal health regulation. First, the agency may lose credibility with consumers, scientists, and the food industry. Second, if the agency is forced to pursue trivial as well as significant risks, it may be incorrectly setting its priorities and misusing its resources, since the nation's capacity for toxicological testing is limited to a few hundred compounds a year. Third, the agency may needlessly discourage industry incentives necessary to ensure a safe, plentiful, varied, and economical food supply. Fourth, the agency's actions might even cause an increase in health risks if a useful substance were eliminated and replaced by one that has not been studied over a long period of time. And fifth, a full scientific inquiry into understanding carcinogenic mechanisms is not encouraged.

Although the need for reform is strong, the risks of revising a statute as complex as the Food, Drug, and Cosmetic Act are also real. The present act may have discouraged the development of some new food products, but little has been compromised in terms of the nutritional quality of the food supply or overall safety protection. It is essential that revisions do not impair the FDA's ability to ensure that our food supply is as safe as, if not more safe, than the present one. Furthermore, it is important to recognize, for instance, that it would not be wise for Congress to rewrite the food safety provisions simply to ensure the continued use of a specific substance such as nitrites or foods with a special role when a more limited provision may solve the problem.

The Statutory Framework

At present the Food, Drug, and Cosmetic Act defines nine major categories of substances, and they are not mutually exclusive. Also, a different regulatory approach is applied to each category (*8*) (Table 1). The temptation is to view this system as an irrational patchwork constructed over the past 75 years by a succession of Congresses oblivious to what their predecessors had done. This temptation should be resisted; although this law is insufferably complex, most of the distinctions it makes are fundamentally sound.

The first federal food law, the Pure Food and Drugs Act of 1906 (*9*), prohibited the marketing of any food containing an "added" poisonous or deleterious substance that "may render such article

injurious to health." It did not, however, give authority to regulate harmful substances that were naturally occurring or to require proof of safety before marketing. In 1938, Congress enacted the federal Food, Drug, and Cosmetic Act (*10*), which divided harmful substances into those that were "added" and those that were "not added." "Added" substances, according to the FDA, are those substances that are "not inherently components of food." Foods containing "added" substances are adulterated, according to section 402 of the 1938 act, if the FDA shows that the substance "may render [the food] injurious to health." "Not added" substances are those that are inherent components of foods such as the oxalic acid in rhubarb, tea, cocoa, and spinach. Foods containing such substances are adulterated, according to section 402, if the FDA can show that the presence of a substance renders food "ordinarily injurious to health." Under section 406 of the 1938 act, the FDA can permit the use of substances that are required to produce food or are unavoidable in its production that would otherwise be banned under section 402. The scope of section 406 is unclear—certainly pesticides were to be so treated, and the application of this section to environmental contaminants by the FDA appears to be justified (*11*). The meaning of such phrases as "required in the production" and "cannot be avoided by good manufacturing practice" is open to question. In 1954, Congress removed pesticides from section 406 and created section 408 for them, but left section 406 intact.

Until the enactment of the Food Additives Amendment of 1958 (*12*), the burden of proving that a substance was unsafe rested with the FDA. Thus, a substance might be in use for many years before the FDA could show that it was harmful. The 1958 amendment shifted the burden to the manufacturer and established, in section 409, a premarketing approval process for substances intended for use in food. Under the new statute, substances would have to be shown to be safe by the manufacturer before they could be used. The provisions of sections 402 and 406, regulating "added" substances, remained in the act.

Section 409 applies only to food additives. "Added substance" and "food additive" are not synonymous terms. In fact, most of the confusion about the current law stems from the legal definition of a "food additive," which includes all substances whose intended use can "reasonably be expected to result" in their "becoming (directly or indirectly) . . . component[s] of food." By this definition, section 409 applies not only to direct additives but also to indirect ones such as packaging materials whose components may migrate into food, animal drugs that may leave detectable residues in food-producing animals, and, under certain interpretations, environmental contaminants such as pesticide residues. The term "food additive" is not limited to synthetic chemicals but includes agricultural commodities as well. A potato

Table 1. Categories of food substances.

Food categories	Statutory section	Statutory safety standards	Examples
1) An added poisonous or deleterious substance	402	The food is adulterated if the poisonous or deleterious substance may render the food injurious to health.	Mercury in fish; aflatoxin in peanuts
2) A naturally occurring poisonous or deleterious substance	402	The food is adulterated if the poisonous or deleterious substance renders the food ordinarily injurious to health.	Inherent constituents of food such as solanine in potatoes, oxalic acid in rhubarb
3) An added poisonous or deleterious substance that is required in the production of food or cannot be avoided by good manufacturing practice	406	A tolerance may be set that takes into account the extent to which the use of such substance is required or cannot be avoided, at levels necessary to protect the public health.	Environmental contaminants such as polychlorinated biphenyls in fish
4) A food additive	409	The substance must meet the requirements of the general safety clause (the legislative history defines safe as "reasonable certainty of no harm") and the Delaney anticancer clauses.	Intentional food ingredients such as saccharin; indirect food additives such as food-packaging migrants
5) A generally recognized as safe (GRAS) substance	201(s)	The substance is safe if it is generally recognized, among experts qualified by scientific training to evaluate its safety, as having been shown through scientific procedures or, for substances used prior to 1 January 1958 through experience based on common use in food, to be safe under the conditions of intended use.	Salt, sugar, vinegar
6) A prior-sanctioned substance	201(s)(4)	The food is adulterated if the prior-sanctioned substance may render the food injurious to health.	Nitrites in meat and poultry; caffeine in soft drinks
7) A pesticide chemical	408	The chemical must be safe for use: appropriate considerations must be given to, among other things, the production of an adequate, wholesome, and economical food supply.	DDT
8) A color additive	706	The substance must meet the requirements of the general safety clause and the Delaney anticancer clause.	Red dyes 2 and 40
9) An animal drug residue	512	The substance must meet the requirements of the general safety clause and the Delaney anticancer clause, modified for animal drug residues, which permits the use of carcinogenic animal drugs if no residue of the drug can be found in any edible portion of the treated animal.	Nitrofuran residues in cattle; diethylstilbestrol residues in cattle

may be considered a food additive when added to a canned stew.

Two types of substances are not considered to be food additives. First, certain common substances such as salt, sugar, and vinegar are in a separate legal category known as "generally recognized as safe" (GRAS) substances (*13*). Second, substances that were granted a sanction prior to the enactment of the Food Additives Amendment could continue to be used (*14*); these are substances for which the FDA issued opinions acknowledging their safety for use in food.

Once a substance is characterized as a "food additive," the premarket approval process as well as the general safety and Delaney anticancer clauses of section 409 apply. Section 409 prohibits the use of a food additive unless a regulation has been issued by the FDA that prescribes permissible terms for its use. The general safety clause states: "No such regulation shall issue if a fair evaluation of the data before the Secretary fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, shall be safe." The safety clause is immediately followed by the Delaney anticancer clause which reads: "Provided, that no additive shall be deemed safe if it is found to induce cancer when ingested by man or animal, or, if it is found, after tests which are appropriate for the evaluation of food additives, to induce cancer in man or animal. . . ." Substances not classified as food additives, such as GRAS or prior-sanctioned substances, may be regulated under section 402 if the FDA can meet the burden of proof required by the "may render injurious" test.

After the enactment of the Food Additives Amendment, Congress passed the Color Additive Amendments of 1960 (*15*) and the Animal Drug Amendments of 1968 (*16*). These amendments established independent frameworks for the regulation of color additives and new animal drugs. Like section 409, the color additive and animal drug provisions each contain a safety and anticancer clause. However, section 512(d)(1)(H)—called the DES Amendment because it was enacted to allow the continued use of diethylstilbestrol (DES) in animals—enables the agency to permit the use of carcinogenic animal drugs if no residue of the drug can be found in any edible portion of the treated animal.

Two federal statutes govern the regulation of pesticide residues in food. The Insecticide, Fungicide, and Rodenticide Act requires all pesticide products to be registered before they are marketed, but first it must show that the product will not pose unreasonably adverse effects on the environment after economic, social, and environmental costs and benefits of use are taken into account. The Food, Drug, and Cosmetic Act, as amended by the Pesticide Chemical Amendments of 1954, created section 408, which establishes tolerances for pesticides residues on raw agricultural commodities that will not endanger the public health. In setting tolerances, considerations such as the need for the production of an adequate, wholesome, and economical food supply must be taken into account.

Unlike section 409, which regulates food additives, section 408, which regulates pesticides, does not contain an anticancer clause but does permit the balancing of risks and benefits.

The Environmental Protection Agency has the authority for setting pesticide tolerances and for pesticide registration; the FDA has the authority for monitoring pesticide residues in foods and for removing from interstate commerce foods that have pesticide residues exceeding the tolerance established by the Environmental Protection Agency.

Rationale for Food Categories

Debate on reforming the existing statute will center on the nine categories of food substances. The Food Safety Panel of the National Academy of Sciences has already recommended that a single standard of safety should apply to all food substances (*17*). Depending on the risk posed by the substance, an appropriate regulatory strategy would be implemented. With this approach all substances are evaluated on one scale—risk.

Practical procedural problems that confront the FDA, however, point to the value of retaining some of the existing categories of food substances. Several categories are defined in terms of how they enter the food supply (for example, direct food additives, environmental contaminants, and naturally occurring substances), and the separation of food substances into these categories reflects, in part, the limitations of the FDA's ability to control exposure or use. The other categories reflect a judgment concerning the practicality of imposing a premarket approval process, the amount of data likely to be available, the likelihood of a proponent for the substance who could assume the burden of toxicological testing, as well as the priority that the substance should have for regulatory attention. Fundamental decisions about risk and benefit are reflected in the different standards imposed on the different categories of food substances. For example, the "ordinarily injurious to health" test applicable to naturally occurring substances requires a greater showing of potential harm than the general safety clause that applies to "food additives."

Two categories have raised considerable concern: the GRAS and prior-sanction categories. The GRAS category reflected congressional beliefs that common substances, such as sugar and salt, should continue in use if experts generally recognize the substance as safe. Thus toxicological testing is forestalled unless some question arises concerning the substance's safety. If the FDA determines that a substance is not GRAS, the burden of proof falls on the manufacturer to demonstrate that the substance meets the safety standard of section 409.

The prior-sanction category, in which substances that the FDA approved before enactment of the 1958 act were grandfathered into use, shifts the burden of ensuring safety to the FDA. Although the safety standard that regulates these substances, the "may render injurious to health" test of section 402, is not appreciably different from the general safety clause of section 409, placing the burden on the FDA to show that harm may occur rather than on the manufacturer to show that the substance is safe, it may determine whether the substance remains on the market. The fact that the FDA had once assured the manufacturer that the substance could be marketed may in part justify the shifting of the burden to the FDA. On the other hand, many of the sanctions were issued at a time when toxicological testing was less sophisticated and the agency knew of no hazard associated with the substance. Nonetheless, the elimination of the prior-sanction exception would create substantial administrative difficulties (*18*).

The Definition of Safe

The general safety clause, which requires that "the proposed use of the food additive . . . be safe," is one of the provisions of the current act most frequently invoked by the FDA. The statute does not specify the meaning of safe, but the legislative history of the 1958 amendments in both the House and Senate shows that safety was equated with proof of "a reasonable certainty of no harm." It also stated that such a clause "does not—and cannot—require proof beyond any possible doubt that no harm will result under any conceivable circumstance" (*19*). The sponsor of the House bill stated that while the standard

did not require proof beyond any possible doubt, it does require proof to a "practical certainty," after "the most searching analysis by pharmacologists and other scientists" (*20*).

This concept of safety does not require more than science can provide, since Congress recognized that there are always risks that are unsuspected. It is not clear, however, whether the concept permits the FDA to ignore a trivial risk once it has been discovered. Those who support a zero-risk interpretation of the general safety clauses hold the view that any risk, no matter how insignificant, is inconsistent with a finding of "no harm." The contrary view, that the safety concept permits the FDA to ignore trivial risks, is that "no harm" is not synonymous with "no risk" and that the "reasonable certainty" portion of the standard implies an acceptance of some risk.

The realistic regulation of foods and food substances requires that some risk be accepted. But how much risk is acceptable and how should such risk be measured (*21*)? The FDA's methods for assessing risk are different for carcinogenic and noncarcinogenic substances. Noncarcinogenic toxicities are regulated with the aid of arbitrarily determined, but widely accepted, safety factors. These safety factors are designed to ensure a safe margin of error for the uncertainties inherent in using animal models to predict human disease and to account for differing susceptibilities within the population. An acceptable dose is established by dividing the maximum dose at which no adverse effects are observed by the safety factor (*22*).

The FDA's regulation of carcinogenic risk is largely dictated by the Delaney anticancer clauses, which presume that there is no threshold below which exposure to a carcinogen is safe. But the detection of trace amounts of potentially carcinogenic substances resulting from the migration of packaging substances, environmental contaminants, or drug residues in food-producing animals has led the FDA, in the opinion of some experts, to adopt new operational definitions of safety for these types of substances (*23*). Using quantitative risk assessment, statistical techniques that estimate the number of cancer deaths that would result from actual exposure levels (*24*), the agency accepts a one-in-one-million lifetime risk of cancer as an acceptable upper level of risk. A lifetime risk of that magnitude has been considered by some to be so small that it may be considered "safe" (*25*). Such advocates of risk assessment, including the FDA, argue that the one-in-one-million upper level cannot be interpreted as an actuarial risk and does not mean that one out of every one million persons will die from exposure to the substance. They argue that a number of conservative assumptions, including assumptions of extreme overuse, have been built into the methodology and that the one-in-one-million upper level represents a negligible risk that is functionally equivalent to zero. Whether a further reduction in risk will provide the public with any significantly greater degree of protection is open to question.

Those who object to the use of quantitative risk assessment argue that it is imprecise and that the actual risk of cancer may be substantially larger or smaller than the estimates predict (*26*). They express further concern that the extrapolation does not take into account cumulative exposures from different substances. Others consider that quantitative risk assessment should be used only in assessing substances for which human exposure is small enough so that any actual variation from the risk estimate would not cause undue harm.

It is widely agreed that quantitative risk assessment can be useful in comparing risks from different carcinogens but is not useful as an indicator of absolute risk.

If it can be agreed that some risk is unavoidable, then its regulation will require assessment, whether quantitative or qualitative. Perhaps the most appropriate type of risk assessment, as one commentator has emphasized, is one that is not limited to deriving numerical estimates of the safety margin or the probability of injury but includes a full description and evaluation of the risk, including the qualitative and quantitative uncertainties that underlie the hazard and exposure estimates (*27*). There are other approaches as well, such as scoring systems that rank carcinogens according to relevant toxicological data from animal and genotoxic studies (*28*). But since no single method of risk assessment has been perfected, Congress would do well neither to endorse nor require any particular methodology in this area.

An important question is whether the statute should be amended to include an explicit definition of safe (*29*). A new legislative standard would both clarify the standard to which the FDA should adhere and legitimize the agency's actions. Much of the current debate has centered on alternatives to the "reasonable certainty of no harm" standard. One proposal has defined safety as "the absence of significant risk," another as "reasonable certainty that the risks are insignificant," and a third as "reasonable certainty that the risks are negligible." Still another keeps the existing definition of safe "as reasonable certainty of no harm" but provides that "no harm may be demonstrated by showing that the risks of harm are negligible" (*30*). All these proposals suffer from lack of definition, but a more precise definition might require a more quantitative than qualitative approach, an issue that these proposals have attempted to avoid. The decision of what is an insignificant or negligible risk would be delegated to the FDA. How much discretion the FDA should have is an important issue for debate.

The Delaney Clauses

Few statutory provisions have generated as much controversy as the anticancer clauses (*5, 31*). They have rarely been invoked—first in 1967 against Flectol H (polymerized 1,2-dihydro-2,2,4-trimethylquinoline) a component of food-packaging adhesives, and again in 1969 against the additive 4-4′-methylenebis(2-chloraniline). Several recent efforts to have substances withdrawn from use, including chloroform, diethystilbestrol, saccharin, trichloroethylene, and nitrites, have relied on the anticancer clauses to some degree.

The Delaney anticancer clauses traditionally have been viewed as unimportant in the FDA's overall statutory scheme and as being redundant with the general safety provisions (*32*). But detection of many trace constituents in a large number of foods, coupled with the development of methods for assessing risk, have stimulated debate about whether the general safety clauses or the anticancer clauses should be applied in agency decisions. A major issue is whether a carcinogen that either is found only in trace quantities or is weakly potent in test animals but accounts for minimal human exposure can ever be considered safe because it presents only an insignificant risk.

The anticancer clauses have been interpreted as prohibiting the use of a food additive, in any concentration, that induces cancer in man or animals. The decision as to whether the substance induces cancer and what tests, in addition to ingestion studies in man or animals, are appropriate to determine carcinogenicity, rests with the scientific judgment of the agency. The clauses are silent on many scientific issues, including whether they are applicable to substances that produce tumors only when tested in large quantities.

A general criticism directed at the anticancer clauses is that they fail to incorporate any concept of risk, as do the general safety clauses. In addition, the anticancer clauses give no discretion to the FDA to consider the extent of human exposure. At the time of their enactment, the rationale for this approach was that it was impossible to establish a safe dose—a threshold—for any cancer-producing substance. It is not clear whether such a threshold will eventually be found at the molecular level, but those who criticize the inflexibility of the anticancer clauses argue that significant progress has been made in assessing carcinogenic risk; they argue that not all levels of exposure to a carcinogen are equally risky and that different carcinogens pose different risks at the same exposure level. The argument continues that risk decreases with decreased exposure, that there is a finite exposure level at which risk becomes so small that no public health benefit would be achieved by further reduction of exposure, and that an exposure level that does not exceed the upper boundary of acceptable risk for a population can be estimated quantitatively (*33*).

Another criticism of the anticancer clauses is that they require a substance to be classified as either a carcinogen or a noncarcinogen. Because test data submitted to the FDA have seldom shown unequivocally that a substance induces cancer, prolonged and at times bitter disputes concerning the significance of the test results have often ensued. If substances could be evaluated on the basis of the risks they pose, the difficulties classifying a substance as either a carcinogen or noncarcinogen might be alleviated.

The third major criticism of the clauses is that they do not stimulate complete scientific inquiry. There is an underlying assumption that all animal carcinogens pose unacceptable risks to humans. Thus, although the FDA is given substantial discretion in evaluating methods of testing, interpreting test results, and determining whether a substance induces cancer, it is unclear whether the FDA could decline to regulate an additive because, for example, the animal models used in the test are not applicable to humans since there are major differences in metabolism. The Delaney anticancer clauses may indeed foreclose consideration of pharmacokinetic, metabolic, or other scientific data, but it is not clear that such data currently exist to justify the conclusion that a substance that induces cancer in animals does not present a risk to humans.

Despite their deficiencies, the Delaney anticancer clauses have served to focus attention on cancer as a serious health problem. Some argue that a high standard of safety should be applied in the regulation of food substances because a majority of additives are consumed involuntarily and that striving toward zero risk is worthwhile, even if such a goal is unattainable. They oppose efforts to make quantitative extrapolations of risk to humans from animal data but rather support the approach of the Delaney clauses, which require only a qualitative interpretation of animal data.

Politically, repeal of the Delaney anticancer clauses is unrealistic. To the public, the clauses symbolize the commitment of the federal government to protect its citizens from health risks. Several approaches toward revising the Delaney anticancer clauses have been suggested. Each attempts to balance political realities with the knowledge that it is not possible to demand a zero-risk standard.

One approach proposed is to revise the clauses so that they operate as a presumption against the approval or continued use of an additive shown to cause cancer. A manufacturer could rebut the presumption by showing that the substance posed a trivial risk and that its use was safe. Evidence concerning the potency of the substance, the level of human exposure, the mechanism by which the substance causes cancer, and the relevance of the animal tests to humans could be presented. Those who object to this approach argue that a rebuttable presumption has the same effect as repealing the clauses. Those who support this approach argue that such an approach is not tantamount to repeal of the clauses because the burden of showing that the use of a presumptive carcinogen is safe would be a difficult one.

A second approach would be to amend section 406, traditionally limited to regulating environmental contaminants, to include specific additives that are essential constituents of foods and that have a long history of use. As noted earlier, section 406 permits the FDA to establish tolerances for added poisonous or deleterious substances whose use "is necessary in the production" of specific foods.

A third approach would limit the categories of food substances to which the Delaney anticancer clauses could be applied. Through administrative action, the FDA has already limited the jurisdiction of the clauses—environmental contaminants, for example, are regulated under section 406, and the FDA has proposed that trace constituents of foods and food contact substances be regulated under the general safety clause (*34*). One court has shown support for limiting the jurisdiction of the anticancer clauses: in *Monsanto* v. *Kennedy* (*35*), the court suggested that a substance (in that particular case, a migrating packaging material) that is present only at a de minimus level need not be regulated as a food additive and thus need not be subject to the anticancer clause.

Various categories of substances could be defined and removed from the jurisdiction of the Delaney anticancer clauses: for example, basic and traditional foods, substances in food-packaging materials, and substances that may possess particular benefits. Substances that are directly added to food, that can be eliminated without undue harm to the food supply, and that do not possess any particular benefits could remain subject to the anticancer clauses. The desirability of an approach that excludes certain categories of substances from the reach of the Delaney clauses may depend on definition of the category and the homogeneity of the types of substances in it—whether all, not simply some, substances in the category should be exempted.

One possibility would be to have the clauses cover direct additives but allow risk assessment for indirect ones. In this way, most low-level risks would be evaluated by risk assessment, since most indirect additives are present in low concentrations. The intentionally or directly added substances would remain under tighter scrutiny. A major criticism of such an approach is that similar risks may be subject to different standards of safety.

Consideration of Benefits

The current statute does not give the FDA authority to compare both the risks and benefits of a food additive. In fact, under the provisions of the 1958 amendments, no consideration of benefits is permitted, and the general safety clauses allow only for consideration of potential harm. However, the FDA may indirectly take benefits into account by, for instance, not relying as heavily on the results of a questionably positive study when confronted with an additive that has important health and economic benefits. An important issue for debate is whether a well-articulated, carefully delineated, and publicly open process that allows for the consideration of benefits is preferable to the current informal and indirect system.

Risk-benefit analysis has serious limi-

tations (*36*). First, if risk-benefit analysis were mandated for each substance, the review process would become substantially more complex and time-consuming, since the agency has traditionally not concerned itself with the benefit side of the risk-benefit equation. Second, consumer confidence in the safety of the food supply might erode if the benefits the FDA considered did not adequately reflect public values; those who reap the benefits are not necessarily those who assume the risks. Third, blanket discretion for balancing risks and benefits would require the FDA to make social value judgments that are more appropriately within the jurisdiction of the Congress. Fourth, the inability to quantify benefits, especially many of the perceived benefits that result from certain dietary foods, is a major drawback of risk-benefit methodology. And, fifth, there is recognition that the current system, which does not provide for consideration of benefits, has worked well for most substances.

In an effort to avoid many of these difficulties, most of the current legislative proposals would permit risk-benefit analysis for a limited number of substances. Only those with a "long history of use and no reasonably practical substitute" as well as either having a risk greater than that permitted under the general safety clause or triggering the Delaney anticancer clauses would be eligible for such consideration.

Several points need to be highlighted about this approach. First, the eligibility criteria for risk-benefit consideration—that a substance have a long history of use and have no substitute—would encompass substances such as saccharin (at the time of the controversy) and nitrites that have generated the most controversy and for which risk-benefit analysis may be the most appropriate. If a substance is eligible for the risk-benefit approach, the risks must first of all be found to be acceptable on account of the benefits. Then, even if the benefits of some substance outweigh the risks, most proposals would put an upper bound on what would be considered a reasonable risk. Furthermore, Congress would have to clarify what is meant by a "substitute": for example, would a substance that has a replacement, but at five times the cost, be considered to have a substitute? Finally, only substances that cannot meet the safety requirements of the law would be considered here. Questions such as whether the FDA should be required to consider the benefits of substances that at present can meet the safety standards, whether it should approve any additive if an adequate substitute exists, and whether it should evaluate the comparative risks and benefits of alternative substances would not be answered. Of course, any approach that requires the FDA to assess relative risks will not only generate substantial disagreement but will also, from an administrative viewpoint, be inordinately complex.

If benefits are to be considered for substances with a long history of use and no substitute, debate must address what types of benefits should be considered. Most proposals agree that the health benefits of such substances as vitamin C and nitrites should be considered. But should the fact that the additive increases the supply of food, reduces its cost, enhances its flavor, or satisfies certain dietary preferences, including the management of specific diseases such as obesity, also be considered?

A criticism raised about permitting risk-benefit analysis for substances that have a long history of use and no substitute is that industry incentive to develop newer and safer products may be stifled. But the opposite might be true—that the development of a newer, safer product might be encouraged because as soon as a substitute is found, the special status of the original substance would be withdrawn, giving the newly developed product the entire market share. Industry innovation might also be encouraged if the FDA had authority to permit the continued use, for a limited time, of substances with a long history of use, no substitute, and substantial benefits while phasing them out of use. The type and extent of risks associated with any substance allowed on the market because certain benefits make attendant risks acceptable must also be clearly described to consumers (*37*).

Independent Scientific Review

In 1978, the FDA released the results of an animal-feeding study that strongly suggested that nitrites produce cancer of the lymphatic system in test animals (*38*). Two years later, after much public furor, the agency, on the basis of an independent pathological review of original tissues decided that nitrites had not been shown to induce cancer (*39*). This incident clearly demonstrated the need for independent scientific review of important food safety studies.

Requirements for scientific peer review have been established for drugs, biologicals, and medical devices (*40*). But the use of independent scientific review for food additives has been haphazard and not subject to any specific requirements: the National Academy of Sciences has reviewed the safety of saccharin; the Federation of American Societies for Experimental Biology has reviewed the GRAS substances; the National Cancer Institute evaluated the safety of cyclamates; and various groups of outside experts have evaluated red dyes 2 and 40.

Before an independent scientific review process is established for food additives, a series of questions such as the following should be considered. When should the FDA submit an issue for scientific review? At what point in the administrative process should review be conducted? How can delays incurred by an additional administrative requirement be minimized? Which issues should be submitted for review? Should all issues that involve potentially carcinogenic substances be reviewed? Should the review be undertaken by a standing or ad hoc committee? How can the quality of the review be ensured? Should the review always include analysis of the raw data?

There are limitations to the value of any independent scientific review process. Although independent scientists may assist in the resolution of scientific issues, many difficult regulatory decisions that require consideration of policy issues, in addition to the scientific issues, must also be resolved. Moreover, the evidence required in any scientific review process will not be the same as that required for regulatory action by the statute. No matter how diligent, scientific review can never answer the difficult question of how much scientific confirmation the agency needs before it can initiate regulatory action.

The Future of Food Safety Legislation

Passage of a new food safety law will not come about quickly. Members of Congress and their staffs must develop a detailed understanding of this complex subject whose controversial nature will even then make the development of a bipartisan consensus difficult. In addition, jurisdictional questions are bound to arise because two committees in the House of Representatives (the Committee on Agriculture and the Committee on Energy and Commerce) and two in the Senate (the Committee on Agriculture and the Committee on Labor and Human Resources) have overlapping responsibilities.

Before a consensus can be reached,

there must be a thorough examination of the state of scientific knowledge in relevant areas, such as the nature and mechanisms of carcinogenic substances, the predictability of laboratory models for human carcinogenesis, and the reliability of quantitative risk assessment. There must be exploration of the difficulties encountered by the FDA in implementing the current statute. These difficulties include the multiple and often overlapping food categories, the effect of technological advancements on the ability to regulate effectively, and the lack of additional authority to phase out, rather than automatically ban, certain products. But many issues in the food safety debate will also require careful scrutiny of social values, especially issues involving benefits, the level of acceptable risk, and the desirability of certain basic, traditional, and special foods.

As elusive as conclusions might be, Congress must reach them. For without a reasoned legislative approach to the scientific, administrative, and social issues in the food safety debate, the FDA's ability to effectively ensure a safe and plentiful food supply will be in an unacceptably uncertain state.

References and Notes

1. *U.S. Code*, title 21, sections 301–391 (1976). For a general overview of food safety issues, see S. Hartman, D. Porter, E. Withnell, "Food safety policy issues" (Report 81-155-SPR, Congressional Research Service, Washington, D.C., June 1981); U.S. Congress, Senate, Committee on Agriculture, Nutrition and Forestry, *Food Safety: Where Are We?* (96th Cong., 1st sess., 1979), committee print; S. Gardner and T. Larkin, *J. Legislation* **7**, 1 (1980); H. Roberts, *Food Safety* (Wiley, New York, 1981).
2. *Fed. Reg.* **47**, 14464 (2 April 1982).
3. For experimental evidence on the carcinogenicity of many food substances, see National Research Council, *Diet, Nutrition, and Cancer* (Washington, D.C., 1982); B. N. Ames, *Science* **221**, 1256 (1983).
4. D. Kessler, *Univ. Chicago Law Rev.* **44**, 817 (1977).
5. *Fed. Reg.* **38**, 10460 (27 April 1973). Evidence now suggests that selenium may protect against cancer (*3*, pp. 10–12).
6. R. Crandall and L. Lave, *The Scientific Basis of Health and Safety Regulation* (Brookings Institution, Washington, D.C., 1981); L. Lave, *The Strategy of Social Regulation* (Brookings Institution, Washington, D.C., 1981).
7. Two national studies on the safety of saccharin could not document any scientific evidence proving or disproving that use of a nonnutritive sweetener leads to any health benefits [National Academy of Sciences, *Saccharin: Technical Assessment of Risks and Benefits* (Government Printing Office, Washington, D.C., 1978), part 1, chapter 4; Office of Technology Assessment, *Cancer Testing Technology and Saccharin* (Government Printing Office, Washington, D.C., 1977), pp. 33–37].
8. R. Merrill, *Mich. Law Rev.* **77**, 171 (1978).
9. Public Law 59–384, 34 Stat. 768 (1906, repealed 1938). For a history of the 1906 act, see O. Anderson, *J. Public Law* **13**, 190 (1964).
10. Public Law 75–717, 52 Stat. 1046 (1938). For a history of the 1938 act, see J. Young, *J. Public Law* **13**, 197 (1964).
11. R. Merrill and M. Schewel, *Va. Law Rev.* **66**, 1357 (1980).
12. Public Law 85–929, 72 Stat. 1784 (1958). For a history of the 1958 act, see C. Dunn, *Legislative Record of 1958 Food Additives Amendment to Federal Food, Drug, and Cosmetic Act* (Commerce Clearing House, Chicago, 1958).
13. *U.S. Code*, title 21, section 321(s) (1976). A substance can be considered GRAS on the basis of toxicological tests conducted either before or after 1958, or if it has a long history of use prior to 1958. The statute does not require the FDA to be the sole judge of a substance's GRAS status. Such recognition can be conferred by "experts qualified by training and experience" to evaluate the substance's safety. Thus, for example, the Flavor and Extract Manufacturers' Association conducted a review of flavoring substances. In 1969, after the FDA banned the artificial sweetener cyclamate, which had been considered GRAS, the FDA asked the Federation of American Societies for Experimental Biology to reevaluate many of the substances considered to be GRAS. Also see *Fed. Reg.* **41**, 53600 (7 December 1976); Select Committee on GRAS Substances, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **36**, 2527 (1977).
14. *U.S. Code*, title 21, section 321(s)(4) (1976); *Fed. Reg.* **37**, 16407 (12 August 1972).
15. Public Law 86-618, 74 Stat. 397 (1960).
16. Public Law 90-399, 82 Stat. 342 (1968).
17. A formal minority statement, signed by five members, disagreed with the recommendations of the 30-member majority. As interpreted by P. Handler, president of the National Academy of Sciences, the minority believed that only a zero probability of cancer is acceptable; if that probability is greater than zero, the substance should be deemed to be of high risk and removed from the food supply [National Academy of Sciences, "Food safety policy: Scientific and societal considerations" (Washington, D.C., 1979), part 2].
18. If FDA were to eliminate the prior-sanction category, it would have to reclassify these substances either as GRAS or those for which food additive petitions would be required. It would take years for the data to be available from which to make determinations about whether the substances met the safety standards required for food additives.
19. U.S. Congress, House, Committee on Interstate and Foreign Commerce, title, 85th Cong., 2d sess. 28 July 1958, H. Rept. 2284; _____, Senate, Committee on Labor and Public Welfare, title, 85 Cong., 2d sess., 18 August 1958, S. Rept. 2422.
20. J. B. Williams, U.S. Congress, House, *Congr. Rec.* 85th Cong., 2d sess., 13 August 1958, vol. 104, p. 17417; D. Freedman, *Ecol. Law Q.* 7, 245 (1978).
21. W. Lowrance, *Of Acceptable Risk* (Kaufmann, Los Altos, Calif., 1976); R. C. Schwing and W. A. Albers, Eds., *Societal Risk Assessment, How Safe Is Safe Enough?* (Plenum, New York, 1980).
22. *W.H.O. Tech. Rep. Ser. 144* (1958) pp. 1–19; *U.S. Code Fed. Regul.*, title 21, section 170.22 (1981).
23. *Fed. Reg.* **44**, 17070 (20 March 1979); *ibid.*, p. 17093; *ibid.* **47**, 14464 (2 April 1982).
24. Testing of suspected carcinogens is usually performed at high doses to increase the cancer risk. In quantitative risk assessment, data from the high-dose bioassays are used to estimate the risk at low doses. Because different mathematical assumptions underlie the various models used to estimate the risk, each model gives a different dose-response curve. Most models fit the experimental data well in the high-dose range, but in the low-dose range some models assume the risk of cancer decreases proportionally to a decrease in dose (that is, the dose-response relation is linear), and other models assume that there is a threshold dose below which there is no risk. In addition to extrapolation from high to low doses, extrapolation is also necessary from laboratory animals to humans. Most methods assume that humans are as sensitive to developing cancer as the most sensitive laboratory animal. Food Safety Council, *Proposed System for Food Safety Assessment* (Washington, D.C., 1980); Office of Technology Assessment, *Assessment of Technologies for Determining Cancer Risks from the Environment* (Government Printing Office, Washington, D.C., 1981).
25. *Fed. Reg.* **46**, 15500 (6 March 1981).
26. In estimating the human risk from saccharin ingestion, the National Academy of Sciences cited ten different statistical models for extrapolation. Depending on the model used, the estimates ranged between 0.22 and 1,144,000 lifetime cases of bladder cancer that would result from the consumption of one bottle of diet soft drink per day by 220 million persons over their lifetime [National Academy of Sciences, *Saccharin: Technical Assessment of Risks and Benefits* (Washington, D.C., 1978), part 1].
27. J. Rodericks, in *Proceedings, Risk Assessment Symposium* (Cosmetic, Toiletries and Fragrance Association, Washington, D.C., 1982), pp. 9–14.
28. R. A. Squire, *Science* **214**, 877 (1981).
29. P. Hutt, *Legal Times of Washington*, 27 April 1981, p. 28; S. Pape and M. Taylor, *ibid.*, 25 May 1981, p. 34.
30. S.1442 and H.R. 4014, 97th Cong., 1st sess. (1981); U.S. Congress, Senate, *Congr. Rec.*, 97th Cong., 1st sess., 25 June 1981, vol. 127, p. S7130; H.R. 5491, 97th Cong., 2d sess. (1982); U.S. Congress, House, *Congr. Rec.*, 97th Cong., 1st sess., 9 February 1982, vol. 128, p. H328; S. 1938 and H.R. 4121, 98th Cong., 1st sess. (1983); U.S. Congress, Senate, *Congr. Rec.* 98th Cong., 1st sess., 6 October 1983, p. S. 13778; U.S. Congress, Senate, Committee on Labor and Human Resources, "Staff working draft," 20 April 1982, committee print.
31. C. Blank, *Calif. Law Rev.* **62**, 1084 (1974); S. Epstein, *Ecologist* **3**, 424 (1973); B. Oser, *Prev. Med.* 2, 150 (1973); M. Schneiderman and N. Mantel, *ibid.*, p. 165; P. Amabile, *Northwest. Univ. Law Rev.* **73**, 1090 (1979); U.S. Congress, House, Committee on Appropriations, Subcommittee on Agriculture, Environmental and Consumer Protection, *Hearings on Agriculture—Environmental and Consumer Protection Appropriations for 1975*, 93rd Cong., 2nd sess., 1975, part 8; General Accounting Office, *Regulation of Cancer-causing Food Additives—Time for a Change?* (HRD-82-3, Washington, D.C., 1981).
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33. J. Rodericks, testimony before the U.S. Senate, Committee on Labor and Human Resources, *Hearings on Oversight of Food Safety Legislation*, 98th Cong., 1st sess., 9 June 1983; Office of Technology Assessment, *Assessment of Technologies for Determining Cancer Risks from the Environment* (Government Printing Office, Washington, D.C., 1981).
34. *Fed. Reg.*, **47**, 14464 (2 April 1982).
35. 613 F. 2d 947 (D.C. Cir. 1979).
36. R. Merrill, *George Wash. Law Rev.* **45**, 994 (1977); R. Cooper, *Food Drug Cosmet. Law J.* **33**, 755 (1978).
37. R. Cooper, in "Product labeling and health risks" (Banbury Report 6, Cold Spring Harbor, N.Y., 1980).
38. "Statement on nitrites," *HEW News* (11 August 1978), P78-28.
39. U.S. Congress, House, Committee on Agriculture, *Hearings on USDA-FDA Announcement on Nitrites and Related Issues*, 96th Cong., 2d sess., 1980.
40. R. Merrill, "Federal regulation of cancer-causing chemicals," report to the Administrative Conference of the United States, 1 April 1982, part 2, p. 48.