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Reasonable Certainty of No Harm: Reviving the Safety Standard for Food Additives, Color Additives, and Animal Drugs*

Daryl M. Freedman**

INTRODUCTION

Americans consume at least 2,000 different food additives, color additives, and residues of animal drugs. These substances—hereinafter referred to collectively as "additives"—have been approved as safe for addition to food by the Food and Drug Administration (FDA), operating under amendments to the federal Food, Drug, and Cosmetic Act passed between 1958 and 1968. The average person consumes more than five

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* This Article is based on a manuscript prepared in November, 1976, as an outgrowth of the author's work earlier that year while an intern with the Natural Resources Defense Council.


1. Under the federal Food, Drug, and Cosmetic Act, a food additive is defined as a substance "the intended use of which results or may reasonably be expected to result, directly, or indirectly, in its becoming a component or otherwise affecting the characteristics of any food." 21 U.S.C. § 321(s) (1970). The statutory definition of a food additive does not include those substances that are generally recognized by experts as safe for their intended uses or those that were "prior-sanctioned" by the Food and Drug Administration or the Department of Agriculture before 1958. Id. Substances generally recognized as safe (GRAS) and prior-sanctioned substances may be marketed without passing the rigorous approval requirements discussed in the text accompanying notes 20-54 infra. GRAS substances, however, become subject to these requirements whenever questions concerning their safety arise. FDA has stated:

   General recognition of safety through scientific procedures under section [321(s)] would therefore require the same quantity and quality of scientific evidence as is required for proof of safety under section [348].


2. A color additive is defined as any "dye, pigment, or other substance" that imparts color when applied to a food, drug, or cosmetic. 21 U.S.C. § 321(t) (1970).

3. A "new animal drug" is defined as "any drug intended for use for animals other than man, including any drug intended for use in animal feed." Id. § 321(w). The definition of new animal drugs does not include substances that are generally recognized as safe. Id. § 321(w)(1), (2).

pounds of these substances each year, and every year more are approved as safe. Additives serve a wide variety of functions in American food; the major categories include flavorizers, colorants, emulsifiers, preservatives, stabilizers, thickening agents, nutrient fortifiers, and substances used to promote animal growth.

The additives in the American diet, however, may pose significant risks to public health. A number of additives currently on the market are suspected of causing cancer, birth defects, and liver, heart, and kidney damage, as well as other health disorders. For example, nitrates and nitrites, used to flavor, color, and preserve such foods as hot dogs, bacon, lunch meats, and smoked fish, are suspected of interacting with other substances to cause cancer. Brominated vegetable oil, a stabilizer used in carbonated beverages, may be responsible for heart, liver, and kidney damage. Antibiotics fed to animals to promote growth are suspected of inhibiting the treatment of serious human infections. Many of these additives have been banned as health risks in various European countries. Consumption of thousands of such additives by human beings over their lifetimes may account for a significant percentage of cancers and other serious disorders.

Americans are exposed to such risks from additives in part because FDA has interpreted the safety standard to which additives must be held in a

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Currently approved additives are listed at 21 C.F.R. §§ 570, 573, 582 (1977) (food additives and animal drugs); 21 C.F.R. § 82 (1977) (color additives).


6. In 1974, 71 new food additives were approved; in 1975, 67 were approved; and during the first six months of 1976, 32 were approved. FOOD CHEMICAL NEWS, Jan. 12, 1976, at 3; FOOD CHEMICAL NEWS, July 12, 1976, at 3.


9. Munro, Middleton, & Grice, Biochemical and Pathological Changes in Rats Fed Brominated Cottonseed Oil for 80 Days, 7 FOOD COSM. TOXICOLOGY 25 (1969). For a popular discussion, see M. Jacobson, EATER'S DIGEST, supra note 7, at 82-85. For further discussion of brominated vegetable oil, see text accompanying notes 84-90 infra.


manner that permits additives to be marketed even when serious questions exist concerning their safety. Moreover, the agency, several courts, and some commentators have maintained that the proper safety standard for these substances is "relative safety"—a standard that permits additives of questionable safety to be marketed so long as their benefits are judged to exceed their risks.

This Article examines the safety standard established in the 1950s and 1960s by amendments to the federal Food, Drug, and Cosmetic Act for food additives, color additives, and animal drugs. The Article demonstrates that the safety standard required by these amendments is "reasonable certainty of no harm." Contrary to the administrative, judicial, and expert opinions mentioned above, this standard does not permit the marketing of additives about which there are serious questions of safety, nor is this standard consistent with a "relative safety" approach. The Article examines and criticizes current administrative and judicial interpretations that permit the evaluation of benefits to enter into the approval decision and sanction the marketing of additives of questionable safety. The Article also explores the reasons for adhering to the reasonable certainty of harmlessness standard. Finally, the Article recommends changes in the current policies and practices of FDA, as well as one statutory change. These changes would help ensure that our food would be as safe as the federal Food, Drug, and Cosmetic Act requires.

I

THE STATUTORY SAFETY STANDARD FOR FOOD ADDITIVES, COLOR ADDITIVES, AND ANIMAL DRUGS

The original federal food safety legislation of 1906 prohibited marketing "adulterated" food, defined as food containing "poisonous or deleterious" substances.13 The degree of health protection afforded by the old law was limited in large part because FDA could not prevent the marketing of a food until it could demonstrate the harmfulness of the food to a district court by a preponderance of the evidence.14 As food production became technologically more complex, the number of substances intentionally added to food increased. Also, over time, there was increased public concern about the long-term hazards of foods, which were far more difficult to demonstrate than the acute illnesses that motivated passage of the 1906 act. Because of these changes, the burden on FDA became increasingly onerous, leaving the public progressively less well-protected.

14. 104 CONG. REC. 17,414 (1958) (letter from Elliot Richardson, Assistant Secretary of Health, Education, and Welfare, to Oren Harris, Chairman of the House Committee on Interstate and Foreign Commerce), reprinted in LEGISLATIVE RECORD OF 1958 FOOD ADDITIVES AMENDMENT TO FEDERAL FOOD, DRUG, AND COSMETIC ACT 39 (C. Dunn ed. 1959) [hereinafter cited as LEG. RECORD].
Through amendments to the federal Food, Drug, and Cosmetic Act enacted in the late 1950s and in the 1960s, Congress sought to provide consumers with greater protection from the addition of harmful substances to food. Congress made two major changes in prior law. First, Congress shifted the burden of proof of safety to the proponent of the use of an additive. Second, Congress defined a highly protective standard of safety for the proponent to meet. The 1958 Food Additives Amendment, the 1960 Color Additives Amendment, and the 1968 Animal Drug Amendments establish that the addition of any of these substances to food renders it adulterated, unless the proponent has demonstrated to FDA that the substance is safe when measured against the new rigorous standard.

A. The Safety Standard for Food Additives

Under the 1958 Food Additives Amendment, only food additives that are specifically approved by regulation may be marketed. FDA may not issue such a regulation unless the proponent of use of the food additive demonstrates "that the proposed use of the food additive, under conditions of use to be specified in the regulation, will be safe." 19

The statute itself does not specify the meaning of "safe," but the legislative history supplies the critical definition. The House and Senate reports on the Amendment state that "safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive." 20

By establishing a standard of reasonable certainty of harmlessness, Congress meant to ensure—to the extent that was scientifically feasible—that no harm would result from the proposed uses of additives. Congress recognized that absolute certainty of harmlessness (zero risk) was impossible to achieve.

The concept of safety . . . does not—and cannot—require proof beyond any possible doubt that no harm will result under any conceivable circumstance.

This was emphasized particularly by the scientific panel which testified before the subcommittee. The scientists pointed out that it is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of any chemical substance. 21

\[\text{19. Id. § 348(a).}\]
\[\text{20. Id. § 348(c)(3)(A).}\]
The sponsor of the bill, Representative Williams, reiterated that while the bill does not require proof of harmlessness "beyond any possible doubt," it does require proof to a "practical certainty." He made clear that this strict standard requires "the most searching analysis by pharmacologists and other scientists" to discover potential risks. Therefore, in adopting "reasonable" rather than "absolute" certainty as the standard, Congress did no more than concede the limits of scientific inquiry; the standard chosen demands only that which science reasonably can provide.

In acknowledging the limits of science, Congress thus recognized that every substance inevitably carries some risk that it will cause unsuspected harm. Accordingly, Congress did not intend to ban additives that have only these "residual" risks. At the same time, the reasonable certainty

23. 104 CONG. REC. 17,418 (1958) (statement of Representative John Bell Williams), reprinted in LEG. RECORD, supra note 14, at 45. In hearings on the House Bill, the General Counsel of FDA testified that the best scientists can do is to be "reasonably sure" that a chemical will be safe for its proposed uses. Hearings on H.R. 4475, H.R. 7605, H.R. 8748, H.R. 7607, H.R. 7764, H.R. 8271, H.R. 8275 Before the Subcomm. on Health and Science of the House Comm. on Interstate and Foreign Commerce, 84th Cong., 2d Sess. 213 (1956) [hereinafter cited as 1956 Hearings]. This is an early variant of the phrase that Congress adopted to give meaning to the statutory safety standard.


25. As scientific knowledge increases, the range of risks to which additives are suspected of contributing and the sensitivity of testing techniques increases. Therefore, over time, there may be new requirements to test for types of risks not formerly considered, in accordance with methodologies only newly developed.

26. The judgment as to the extensiveness of the scientific inquiry required to discover potential risks necessarily involves a policy evaluation of the appropriate trade-offs between the benefits of possible scientific studies and their costs. This kind of evaluation bears on such questions as, for example, whether scientific testing of new additives should be extended to include testing for possible teratogenic and mutagenic effects.

Every additional study required offers the potential benefit of additional information about risks which, if discovered, could be avoided. But every additional study exacts financial costs. Since Congress presumably was not interested in devoting all available resources to the scientific testing of food additives, a policy decision must be made as to what financial costs are justified. But once the required scientific tests have been designated, the determination as to whether an additive is safe does not necessitate an evaluation of the additive's benefits. See text accompanying notes 30-36 infra.

27. A number of factors account for the existence of risk from unsuspected harms. First, since scientific study of the effects of additives is based on experiments involving limited numbers of animals, the limited sample sizes necessarily create a statistical sampling error—even where no harm is observed, experiments do not provide complete assurance that no harm exists. This source of unsuspected harms was suggested by George Larrick, a former Commissioner of FDA, in hearings concerning food additive bills: "So long as our methods of testing involve complex chemical and biological methods of analysis and identification, there will be a residual risk of permitting use of some chemicals." 1956 Hearings, supra note 23, at 195 (emphasis added). While such risks are a necessary by-product of reliance on limited sample sizes, the risk of error declines as sample size increases. In part, the sample sizes established by scientific protocols are a function of budgetary constraints. Thus, to some degree, the risk of unsuspected harm due to statistical sampling error reflects financial considerations. See note 26 supra.
standard clearly does not permit the marketing of additives for which known harm or risks are recognized.

Determining whether the reasonable certainty standard has been met is less straightforward when evidence suggests that an additive may be harmful. Risks may be suggested by studies that are not fully conclusive because of methodological shortcomings. Solid evidence of the harmfulness of one substance may call into question the safety of similar chemicals.\textsuperscript{28} At what point is there a question of safety sufficient to violate the reasonable certainty of harmlessness standard? While no hard-and-fast rule may be established, the logic of the statutory standard suggests a way of defining the point at which the standard is not met.

Reasonable certainty of harmlessness does not exist if a substantial portion of the scientific community believes that additional studies of a substance are needed.\textsuperscript{29} So long as additional scientific studies are considered justified, there is no longer certainty, within existing scientific limits, that an additive is harmless.

Moreover, in establishing a reasonable certainty standard, Congress

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\textsuperscript{28} Second, risk of unsuspected harms also results from use of animal rather than human studies. No selection of animals can reflect the full variety of human conditions. The testimony before Congress of William Goodrich, then Assistant General Counsel of FDA, reflected recognition of this source of unsuspected harms. He said:

We, as well as the Food Protection Committee of the National Research Council, recognize that present day scientific methods cannot tell us conclusively that a chemical proposed for use in food will be absolutely safe in all conditions of sickness and health and of youth and old age.

1956 Hearings, supra note 23, at 213. Budgetary constraints also play a role in determining the extent to which the animals selected reflect human conditions. Those animals most closely resembling human beings—monkeys—are generally not selected, while less expensive species such as mice and rats are generally used.

Finally, residual risks also exist because tests are undertaken for only a limited range of types of harm. This is partly because some types of harm are completely unsuspected. For example, until the work of Dr. Benjamin Feingold was recently published, a potential causal link between food additives and the hyperactivity of some children was probably not even contemplated. For a discussion of Dr. Feingold's research, see Feingold, \textit{Hyperkinesis and Learning Disabilities Linked to Artificial Food Flavors and Colors}, 75 AM. J. NURSING 797 (1975). Further, budgetary considerations are again responsible in part for the narrow range of possible harms for which tests are undertaken. For example, while it is known that chemicals in the environment may cause mutagenic effects, such tests are not required for all additives. See note 170 infra. For a more thorough discussion of the sources of uncertainty in toxicological evaluation, see text accompanying notes 149-160 infra.


29. It might be argued that since Congress demanded "the most searching analysis" to discover potential risks, FDA's discretion as to whether to require more studies is constrained by the judgment of the scientific community. If a substantial portion of that community asserted that more testing was needed to establish the safety of a substance, FDA would be precluded from approving that substance for use. FDA would have discretion to require more studies than those judged necessary by the scientific community, but it could not require less. Medical malpractice law provides a precedent for relying on the judgment of a community of experts to establish a scientific standard. See McCoid, \textit{The Care Required of Medical Practitioners}, 12 VAND. L. REV. 549, 558-75 (1959).
FOOD ADDITIVES

implicitly rejected a "relative safety" standard.30 This standard would permit marketing of additives when their benefits exceed their risks, either known or suspected. In adopting a standard that would not permit the marketing of additives for which there are known or suspected risks,31 Congress necessarily judged benefits to be irrelevant to the determination of safety.32

An examination of the well-known Delaney Clause33 provides further evidence that the reasonable certainty of no harm standard does not permit consideration of the purported benefits of an additive. The Delaney Clause, a proviso attached to the generally applicable requirement that food additives be "safe," is specifically directed to risks of cancer. The clause bars the addition to food of any substance that has been demonstrated to cause cancer in man or animal,34 and therefore it does not permit FDA to weigh the purported benefits of a substance against the risk of cancer. As the legislative history of the Delaney Clause makes clear, Congress viewed the specific prohibition of carcinogenic additives as redundant. The Senate report said:

[W]e want the record to show that in our opinion [without the Delaney Clause] the bill is aimed at preventing the addition to the food our people eat of any substances the ingestion of which reasonable people would expect to produce not just cancer but any disease or disability. In short, we believe the bill reads and means the same with or without the inclusion of the clause referred to.35

30. This standard has been incorrectly embraced by the courts, see text accompanying notes 116-132 infra, and has apparently been adopted by FDA. See text accompanying notes 55-113 infra.

31. By permitting the marketing of additives despite the existence of residual risks, Congress implicitly determined that the benefits of these additives, as a class, outweighed such residual risks. It does not follow from this implicit cost-benefit determination that Congress condoned the measurement of benefits against known or suspected risks.

32. The Amendment does require, when FDA sets a tolerance limit for an additive, that the agency determine that the additive actually achieves its intended effects at the proposed levels of use. 21 U.S.C. § 348(c)(4)(B) (1970). Effectiveness, however, is no more than a threshold requirement, a prerequisite to consideration of safety. Both the House and Senate reports stated:

The question of whether an additive produces such effect (or how much of an additive is required for such effect) is a factual one, and does not involve any judgment on the part of FDA of whether such effect results in any added "value" to the consumer of such food or enhances the marketability from a merchandising point of view.


FDA also requires that a GRAS substance perform "an appropriate function in the food . . . in which it is used." 21 C.F.R. § 170.30(h)(2) (1977). A requirement that the substance withstand a risk-benefit analysis was separately proposed by FDA, albeit in derogation of the statutory standard of safety. 41 Fed. Reg. 53,600, 53,601 (1976). See also note 59 infra and accompanying text. The "appropriate function" requirement "is intended simply to require that the ingredient accomplish some technical or physical effect." Id. at 53,602.


34. Id.

Because the Delaney Clause prohibits the consideration of benefits, and because the bill means the same with or without the clause, it follows that the reasonable certainty of harmlessness standard also prohibits the consideration of benefits.36

In a letter to Representative Oren Harris, the Chairman of the House Committee on Interstate and Foreign Commerce, the Assistant Secretary of Health, Education, and Welfare, Elliot L. Richardson, made the same observation:

There are many serious conditions other than cancer that may be caused or aggravated by the improper use of chemicals. It is manifestly impracticable to itemize all of them in a bill. To single out one class of diseases for special mention would be anomalous and could be misinterpreted. Hence, in drafting the Department's bill (H.R. 6747) we chose general language that would restrain any use of an additive that would have any adverse effect on the public health. This approach has been followed in H.R. 13254.

104 CONG. REC. 17,415 (1958), reprinted in LEG. RECORD, supra note 14, at 40.

36. In order to comprehend more fully the stringency of the generally applicable safety standard, it is helpful to compare its effectiveness for controlling potential carcinogens with that of the Delaney Clause.

The Delaney Clause is less effective in controlling additives that are only potentially carcinogenic. Under the Delaney Clause, an additive may be removed from the market only "if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal." 21 U.S.C. § 348(c)(3)(A) (1970) (emphasis added). The requirement that the additive must be "found" to be carcinogenic means that the Delaney Clause will not bar from the food supply an additive about which there is inconclusive evidence of carcinogenicity. Moreover, the requirement that tests be "appropriate" also restricts the kind of evidence that will justify a ban. In contrast, under the generally applicable safety standard, both carcinogens and additives for which there are serious questions of carcinogenicity must be banned, since no such additive could be characterized as reasonably certain not to cause harm. See text accompanying note 29 supra.

With respect to the permitted levels of use of known carcinogens, the relative effectiveness of the two clauses is less certain. The Delaney Clause bars additives at any level of use, even if their carcinogenic effects have only been demonstrated at high-use levels. In apparent contrast, the generally applicable safety standard permits marketing of additives that are demonstrably harmful at high-use levels if there is reasonable certainty of their harmlessness at a proposed lower level of use.

The generally applicable safety standard, however, can be interpreted to be as rigorous as the Delaney Clause with respect to permitted levels of use. In enacting the Delaney Clause, Congress arguably adopted the view that no safe levels of exposure to carcinogens have been established and that in fact a safe dose may not exist. This view is accepted by many cancer experts today. See Hueper, Public Health Hazards from Environmental Carcinogens, Mutagens, and Teratogens, supra note 12, at 698; U.S. Public Health Service, Evaluation of Environmental Carcinogens: A Report to the Surgeon General (1970), reprinted in Hearings on Chemicals and the Future of Man before the Subcomm. on Executive Reorganization and Government Research of the Senate Comm. on Government Operations, 92d Cong., 2d Sess. 180 (1971). Thus, it can be argued that no amount of a carcinogen is reasonably certain to be harmless, and that neither the Delaney Clause nor the generally applicable standard permit any level of carcinogens to be added to food.

At least with regard to the cancer risks of saccharin, which were demonstrated under exaggerated conditions of use, FDA apparently holds that both provisions are applicable. Donald Kennedy, the present FDA Commissioner, stated:

The focus on the Delaney Clause led many people to believe that we would not have acted against saccharin in foods and beverages without this strict provision. This is not true. General provisions of the Food, Drug, and Cosmetic Act say that food additives must be safe. And with the accumulated evidence we now have against saccharin, including cancer findings in each of the last three animal studies, our judgment is that it is not safe for continued use as a food additive. We therefore would have moved to end the general use of saccharin even without the Delaney Clause.
B. The Safety Standard for Color Additives

In 1960, Congress enacted the Color Additive Amendments, which state that color additives may be approved for use in or on food "if and to the extent that such additives are suitable and safe for any such use." The legislative history of these amendments shows that Congress intended to apply to color additives the same safety standard that had been developed for food additives two years before.

Before 1960, only some color additives were treated as food additives and subject to the reasonable certainty of harmlessness standard. Coal tar dyes were subject to a different standard. While they could be removed from the market if found to be harmful at any level of use, FDA bore the burden of demonstrating their harmfulness. Because of the large number of coal tar dyes in use, it was expected that FDA might need as many as twenty years to perform the scientific testing necessary to determine the safety or harmfulness of all of these substances. In 1960, Congress concluded that this delay exposed the public to unnecessary risk. In order to protect the public, Congress established premarket clearance requirements for all color additives, thus shifting the burden of testing to the dye manufacturers. It also required that the safety standard of the Food Additives Amendment be applied to all color additives, including coal tar dyes. The House report stated:

The bill adopts for all colors, and for all color uses covered by it, the basic principle of the Food Additives Amendment of 1958, by providing for the official listing of color additives for any use in or on foods . . . for which they are determined to be safe . . . .


42. While the Color Additive Amendments required all new color additives to be found safe before being formally approved for marketing, the Amendments also established a temporary exemption for colors currently marketed but not yet fully tested. Pub. L. No. 86-618, § 203, 74 Stat. 397 (1960). Such additives were to be provisionally approved, and proponents of their use were given up to two and one-half years to comply with testing requirements. "This maximum period could be extended only where, in a particular case, such extension is necessary to complete the required safety tests for a color and is found consistent with protection of the public health." 106 CONG. REC. 14,357 (1960) (statement of Representative Harris). Because FDA has repeatedly postponed the closing dates for provisional listing of a number of color additives, a provisional list of color additives remains in effect. 21 C.F.R. §§ 82.101, 82.102, 203, .303, .304, .705, .706 (1977).
Accordingly, in providing the standard for withdrawal of approval of a color additive, the House report stated that the conditions are met when "there is reasonable doubt as to the safety of color additives for the cited use." 44

C. The Safety Standard for Animal Drugs

The 1968 Animal Drug Amendments 45 permit the approval of an animal drug for marketing only if adequate tests show that the drug is safe for use under the conditions listed in the proposed labeling. 46 The proponent of the use of an animal drug has a continuing duty to show that it is safe; if new evidence suggests that the drug is no longer shown to be safe, the amendments require withdrawal of the drug's approval. 47 Like the Food Additives and Color Additive Amendments, these Amendments do not themselves further specify the applicable safety standard.

The legislative history of the Animal Drug Amendments shows that Congress intended to apply to these substances the same safety standard that was applied to food and color additives. After 1958, animal drugs that could "reasonably be expected" to become components of, or affect food—such as drugs intended for food-producing animals—were subject to approval as food additives under the reasonable certainty of harmlessness standard. 48 These drugs were also subject to other approval procedures in a complex and fragmented approval process. 49 The 1968 Amendments were enacted in order to reduce this complexity by establishing one "logical coordinated system" 50 and providing "a smoother procedure for handling" approvals. 51 The changes were not intended to alter the existing standard of safety governing animal drugs. As Representative Jarman, the sponsor of the Amendments, stated: "[The bill] would not, in any manner, reduce the rigid

44. Id. at 28. Like the Food Additives Amendment, the Color Additive Amendments contain a Delaney Clause barring the approval of carcinogenic substances. 21 U.S.C. § 376(b)(5)(B) (1970).
47. See id. § 360b(e)(1)(B).
49. Until 1968, all new animal drugs also had been subject to the New Drug Amendments of 1962, principally the provisions for approval. 21 U.S.C. § 355 (1970). In addition, if the animal drug included certain antibiotics, it was subject to special certification provisions. Id. § 357.

For a general description of the procedures preceding and following the enactment of the Animal Drug Amendments in 1968, see Kingma, New Animal Drug Amendments and Implementing Regulations—FDA's View of Their Effect on Sponsors, 26 Food Drug Cosm. L.J. 56 (1971).
controls contained in existing law to safeguard public health." This position is reinforced by similar statements in both the House and Senate reports. Thus, the reasonable certainty of harmlessness standard applies to animal drugs as well as to food and color additives.

**D. Summary of the Statutory Standard**

The statutory safety standard for food additives, color additives, and animal drugs requires that the proponents of use provide evidence that establishes a reasonable certainty that no harm will result from the proposed use of the additives. This standard does not require absolute certainty of harmlessness, but it does limit acceptable harms to the residual risks arising from the limits of scientific knowledge. The standard bars the use of additives whose use raises substantial questions of potential harm, as well as those additives with known risks. It is a one-dimensional standard that does not permit known or suspected risks to be offset or justified by expected benefits.

**II ADMINISTRATIVE AND JUDICIAL INTERPRETATIONS OF THE STATUTORY SAFETY STANDARD**

**A. Interpretations by FDA**

As reflected by a number of its general regulations and specific actions relating to additives, FDA has misinterpreted or failed to apply the rea-
sonable certainty of harmlessness standard. These regulations and actions have sanctioned the marketing of additives about which serious questions of safety have been raised, and have allowed consideration of purported benefits to influence decisions that are meant to turn only on an assessment of risk. Such distortions of the standard have been reflected both in the agency's approval of new additives and in its failure to withdraw additives previously approved.

1. Interpretations Relating to New Approvals

a. FDA regulations

FDA regulations governing the approval of new additives describe the statutory safety standard in several ways. Only the regulation applicable to approval of new color additives clearly adopts the statutory standard. By contrast, FDA regulations governing approval of new food additives and animal drugs have described the relevant standard of safety in a variety of ways that are not necessarily consistent with the legislative standard of reasonable certainty of harmlessness.

The general regulations governing approval of color additives and animal drugs may be treated briefly. The applicable regulation states that a color additive must be "safe," which is defined to require "convincing evidence that establishes with reasonable certainty that no harm would result from the intended uses of the color additive." 55 The regulation governing

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55. 21 C.F.R. § 70.30 (1977).
approval of new animal drugs merely requires "adequate tests... to show whether or not such drug is safe for use." 56 Because no definition of "safe" is provided, the regulation does not reveal the standard or standards of safety being applied.

With respect to the approval of food additives prior to 1971, FDA's regulation had required a "reasonable certainty that no harm will result from the intended use of the food additive." 57 In 1971, without offering an explanation, FDA modified its regulation to require "that no significant risk of harm will result when the substance is used as intended." 58 At best, the alteration effected no change—the "insignificant" risks permitted by the new regulations may only refer to the residual risks allowed under a reasonable certainty of harmlessness standard. It is, however, also possible that this version signaled a weakening of the standard applied to the approval of new food additives. This regulation may reflect FDA's willingness to approve the use of additives that involve known risks of nonserious harms or that involve known risks limited to a small percentage of population. Moreover, FDA has maintained that the benefits of a food additive should be considered in determining whether the additive is "safe." 59 Nevertheless, under the present statutory standard, no known risks are permitted. 60

b. FDA regulatory practices

In general, the history of FDA practices does not reveal how the agency interprets its own regulations. In explaining its approval or denial of applications for the approval of new additives, FDA often states no more than whether the additive has or has not been found to be "safe." 61 At times, however, FDA has explained its decisions concerning approvals with sufficient detail to permit an appraisal of the safety standard applied by the agency. The agency's actions respecting cyclamates and acrylonitrile suggest two quite different approaches to safety.

In 1970, applying the general safety provisions, FDA revoked approval of cyclamates, a type of artificial sweetener, because of evidence that they

57. 21 C.F.R. § 121.1(i) (1971).
58. 36 Fed. Reg. 12,093 (1971) (codified at 21 C.F.R. § 121.1(i) (1972)). The regulation has since been amended to require "a reasonable certainty in the minds of competent scientists that the substance is not harmful." Food Additives, 42 Fed. Reg. 14,483, 14,483 (1977) (codified at 21 C.F.R. § 170.3 (1977)).
59. 41 Fed. Reg. 53,600, 53,600-01 (1976). In FDA's opinion, "the [statutory] term 'safe' is to be given its ordinary meaning, and in its common usage the term is understood to carry an assessment of benefits and risks." Id. at 53,601. However, FDA does not propose to commit itself to "routine formal analysis" of an additive's benefits; "the agency will only occasionally need to take [such factors] into account." Id. Note, however, that FDA had previously refused to take benefits into account when determining whether to withdraw approval of diethylstilbestrol (DES), an animal drug. See note 131 infra.
60. Under the statutory standard no known harms can be considered insignificant. See note 36 supra. Even additives that cause only minor pathologies or pathologies that are likely to occur only in a minor percentage of the population may not be approved.
caused cancer.\textsuperscript{62} Since that time, manufacturers have petitioned FDA to permit cyclamates to be marketed again. In a 1976 statement concerning cyclamates, the FDA Commissioner strongly suggested that the statutory standard does not permit the approval of additives when either known risks or unresolved questions of safety exist. He stated that FDA could not approve the use of a cyclamate if scientists could assure only a ninety-five percent probability that it is not carcinogenic. Saying that he was "looking for a clean bill of health," the Commissioner announced that a "wishy-washy answer" from the experts or a call for additional studies would prevent FDA from approving the sweetener.\textsuperscript{63}

Yet, with respect to plastic beverage bottles made of acrylonitrile copolymer, FDA appears to have misinterpreted the statutory safety standard.\textsuperscript{64} Between 1974 and 1976, FDA approved the use of this substance in beer and soft drink bottles.\textsuperscript{65} Yet in 1974, the agency indicated that there was potentially significant migration of acrylonitrile from the bottle walls to the beverages contained within the bottles.\textsuperscript{66} FDA acknowledged that there were no adequate long-term studies of the effects of acrylonitrile on animals that would support the safety of the substance.\textsuperscript{67} Of the two available long-term studies, both suggested serious harmful effects. One linked acrylonitrile

\textsuperscript{64} Food-contact articles such as plastic bottles are "indirect" food additives if they may "reasonably be expected" to become components of food or affect the characteristics of food. See 21 U.S.C. § 321(s) (1970). See e.g., United States v. Articles of Food, 370 F. Supp. 371 (E.D. Mich. 1974) (pottery dinnerware could contain food additive).
\textsuperscript{65} 39 Fed. Reg. 38,895 (1974) (codified at 21 C.F.R. § 177.1050 (1977)); \textit{id.} at 43,057 (codified at 21 C.F.R. § 177.1030 (1977)); 40 Fed. Reg. 6489 (1975) (codified at 21 C.F.R. § 177.1040 (1977)); \textit{id.} at 40,800 (codified at 21 C.F.R. § 177.1020 (1977)); 41 Fed. Reg. 9545 (1976) (codified at 21 C.F.R. § 177.2910 (1977)). These additives were approved on the grounds that they met the tentative harmless or "no-effect" level set forth in a proposed regulation governing continued marketing under "interim regulations." This no-effect level was the basis for new approvals of additives as safe, even though: (1) the no-effect level was derived from a study deemed inadequate by FDA; (2) the study relied on to establish a no-effect level had suggested that acrylonitrile was a carcinogen, which would call into question whether any safe tolerance level could be established; (3) one of the bases for the proposed interim regulation was FDA's judgment that there was a need for additional studies on toxicity and thus, safe levels of use; and (4) another basis for the proposed interim regulation was the lack of adequate data concerning the level of migration of acrylonitrile over time. For a discussion of the difficulties involved in attempting to satisfy the reasonable certainty standard by promulgating interim regulations which establish new conditions of use, see text accompanying notes 78-107 infra.

Acrylonitrile copolymer is also regulated as an indirect food additive for the following uses, among others: cellophane, 21 C.F.R. § 177.1200 (1977); resinous and polymer coating, \textit{id.} § 175.300; adhesives, \textit{id.} § 175.100; components of paper and paperboard in contact with aqueous and fatty foods, \textit{id.} § 176.170.

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to an increased incidence of cancer in the test animals, and the other, to a progressive weakening of the hind legs of pregnant rats.\textsuperscript{68} Short-term studies at higher doses showed such acute effects as adrenal damage, duodenal ulceration, and increased mortality.\textsuperscript{69} FDA also acknowledged that the World Health Organization believed the data on acrylonitrile to be inadequate to establish an acceptable daily human intake.\textsuperscript{70}

In view of the proponent's affirmative duty to establish the safety of a food additive,\textsuperscript{71} the inadequacy of the data did not permit FDA to allow marketing of acrylonitrile copolymers with reasonable certainty of their harmlessness. Yet, not until March, 1977, did FDA stay the continued use of acrylonitrile in plastic bottles.\textsuperscript{72} In presenting the basis for its stay, FDA cited new evidence of harmfulness; it did not comment on the inadequacy of the data in support of the original approval.

2. \textit{Interpretations Relating to Previously Approved Additives—Interim Status}

With respect to additives already approved for use, no special statutory provision specifies a mechanism for removing from the market those no longer found to be safe.\textsuperscript{73} Once approval for marketing is withdrawn, products containing unapproved additives are deemed to be adulterated,\textsuperscript{74} and become subject to statutory sanctions relating to adulterated foods.\textsuperscript{75} In general, the finding that an additive is no longer safe leads manufacturers and distributors who seek to avoid such sanctions and their attendant publicity to voluntarily remove the additive from the market.

Because of these statutory requirements, FDA was confronted with a regulatory dilemma. A strict interpretation of the safety standard by FDA

\textsuperscript{68} \textit{Id.}


\textsuperscript{71} See text following note 14 \textit{supra}.

\textsuperscript{72} Acrylonitrile Copolymer Beverage Container; Stay of Regulations, 42 Fed. Reg. 13,546 (1977). The District of Columbia Court of Appeals set aside the stay on the grounds that the Commissioner could not stay the regulations until a hearing had been held on the objections of a manufacturer of acrylonitrile containers. Monsanto Co. v. Gardner, [1976-77 Transfer Binder] CCH \textit{FOOD DRUG COS. L. REP.}, ¶ 38,097. Following a formal evidentiary hearing, the Commissioner amended the food additive regulations at issue to eliminate use of acrylonitrile copolymers in beverage containers. Acrylonitrile Copolymers Used to Fabricate Beverage Containers; Final Decision, 42 Fed. Reg. 48,528 (1977). Appeals of this decision were taken by a number of petitioners, and were consolidated. This appeal is now pending. Monsanto Co. v. Kennedy, No. 77-2023 (D.C. Cir., filed Nov. 17, 1977).

\textsuperscript{73} The statute provides only the process governing withdrawal of approval. \textit{See} 21 U.S.C. § 348(b) (1970) (food additives); \textit{id.} § 360(m)(4)(B) (animal drugs); \textit{id.} § 376(d) (color additives).

\textsuperscript{74} \textit{See id.} § 402(a)(2)(C); \textit{id.} § 402(a)(2)(D); \textit{id.} § 402(c).

\textsuperscript{75} These sanctions include seizure, \textit{id.} § 304, and fines or imprisonment for the sellers of such products. \textit{Id.} § 303(a).
could result in the removal from the market of a number of products about which suspicion had been raised, but which had not been conclusively proven to be harmful. From FDA's perspective, this was not feasible. Such a strict interpretation not only threatened to impose severe short-term adjustment costs on the business community, but also threatened to cause a congressional and public relations backlash that jeopardized FDA's credibility. FDA could have been charged with making irresponsible and quick-tempered decisions that were not based on solid evidence of known harms. Yet, on the other hand, FDA had a legislative injunction to withdraw approval of additives that could not be demonstrated to be safe.

FDA's solution—interim regulations—retained the terminology, but not the substance of the statutory standard. In reality, the interim regulations expand the meaning of "reasonable certainty of no harm" by permitting both the continued marketing of additives of questionable safety and the purported balancing of benefits against health risks.

a. Interim regulations for food additives of questionable safety

(1.) The nature of interim regulations

FDA has established "interim regulations" which permit the continued use of food additives about which substantial questions of safety have arisen. Permission for continued use is ostensibly limited to the period necessary for scientific resolution of the safety questions. Sometimes the permitted concentration of the additive is also reduced. The regulation establishing this interim status and FDA's interpretation of the regulation illustrate the invalid "stretching" of the reasonable certainty of no harm standard. The regulation states:

76. Regarding currently approved food additives, FDA stated:

With the vast increase in the quantity of scientific testing and in the sophistication of test methodology, there is virtually no natural or synthetic food substance that cannot be questioned on some technical ground. It would be impossible to require elimination from the food supply of every food substance for which such scientific questions have been or will be raised.

GRAS and Food Additive Status Procedures, 37 Fed. Reg. 25,705, 27,706 (1972). Similarly, with respect to existing animal drugs, FDA stated:

It would be chaotic, and is clearly not feasible, to withdraw approval of all food or drug substances merely because new questions have arisen, new testing is considered scientifically appropriate, or new studies raise issues that require further exploration.


77. See generally Merrill, Risk-Benefit Decisionmaking by FDA, 45 GEO. WASH. L. REV. 994, 1006 n.61 (1977) (stating the purpose of interim regulations).

78. Food Additives Permitted in Food or in Contact with Food on an Interim Basis Pending Further Study, 21 C.F.R. § 180.1 (1977). In some instances the Commissioner has placed an additive on interim status and reduced the level permitted in food, implying that while amounts of the additive permitted in food prior to the interim regulation may not have satisfied the reasonable certainty standard, the additive can satisfy the standard in restricted quantities. See, e.g., Acrylonitrile Copolymers Intended for Use in Contact with Food, 39 Fed. Reg. 38,907, 38,908 (1974) (regulating plastic bottles).
An interim food additive regulation for the use of any food additive may be promulgated . . . when new information raises a substantial question about the safety or functionality of the substance but there is a reasonable certainty that the substance is not harmful and that no harm to the public health will result from the continued use of the substance for a limited period of time while the question raised is being resolved by further study.79

This regulation appears inconsistent with the statutory standard because it indicates that there may be reasonable certainty that an additive is harmless even though "substantial questions" concerning its safety have been recognized and are judged sufficient to warrant additional research. Permission to continue use of an additive would be consistent with the statutory standard only if FDA were to request additional evidence of an additive's safety in spite of the scientific community's judgment that further research is unwarranted. In view of the natural reluctance of the agency to impose heavy testing costs unnecessarily, it is unrealistic to expect such a situation to arise.

The regulation could also operate consistently with the statutory standard if FDA were capable of ascertaining with reasonable certainty before promulgating an interim regulation that a substance is harmless in restricted amounts or for a limited period of time. However, restrictions on the permitted amount of the questionable additives cannot, as a practical matter, satisfy the reasonable certainty of harmlessness standard. Additives are placed on interim regulations only when substantial questions concerning their safety are raised and studies are needed to establish a level at which they do not produce harmful effects. Until additional studies resolve the questions of safety, the establishment of interim tolerance levels is necessarily arbitrary and does not assure reasonable certainty that no harm will result from their use at such levels.80 Similarly, the very evidence that raises a substantial question of safety with respect to an additive and calls for further research also suggests that there may be no basis for establishing with confidence the period during which exposure would be safe. In addition, there is no reason to believe that the "safe exposure" period, if it could be known, would necessarily correspond to the time needed to resolve the questions of safety.81


80. It is possible, for example, that there are no "safe doses," however small, of carcinogens. See note 27 supra.

81. Tests for potential long-term effects might take two to three years. See note 88 infra.
Moreover, while the regulation states that interim regulations shall be applied for "limited" periods of time, the record on interim regulations suggests the contrary. In several cases where interim regulations have expired, indefinite postponements have been granted. Thus, the effect of the regulation and FDA practice is to redefine as safe and marketable those food additives for which there is no reasonable certainty of harmlessness.

As indicated by FDA, considerations of the purported benefits of an additive may influence the decision to place it on interim status rather than to withdraw approval for marketing. Among the criteria for such decisions are "the purpose for which the additive is used, and the availability of alternative ingredients." In considering these two factors, FDA must evaluate the economic importance of the uses of the substance and the quality of substitutes for it. Where the importance of the use or the shortcomings of the substitutes are taken as grounds for permitting continued marketing of an additive, FDA in effect invalidly applies a relative safety standard, trading benefits against risks.

(2.) Interim regulations in practice

FDA's justifications of its decisions to place or retain specific food additives on interim status support the inference that the agency has broadened invalidly the concept of reasonable certainty of harmlessness. This is illustrated in practice by FDA's regulation of two substances: (1) brominated vegetable oil (BVO), a stabilizer used in carbonated drinks; and (2) saccharin, an artificial sweetener.

At least since 1969, there has been a serious case against the safety of BVO. In that year, toxicologists at the Canadian Food and Drug Directorate reported that rats given large doses of BVO over an eighty-day period suffered impairments of the heart, liver, thyroid, testicles, and kidney. In 1970, the World Health Organization's Expert Committee on Food Additives called attention to the cardiac problems of animals fed high doses of BVO, noted the accumulation of bromine in the fatty tissue of both experimental animals and humans, and concluded: "The evidence suggests that a human epidemiological problem could arise from the use of BVO's. . . . BVO's should not be used as a food additive in the absence of evidence indicating their safety." By 1970, BVO had been banned in Sweden and Great Britain. In the same year, acknowledging the results of studies "demonstrating significant biochemical and pathological changes" in animals fed BVO, FDA concluded that the additive could no longer be con-

84. Munro, Middleton, & Grice, supra note 9.
85. M. Jacobson, EATER'S DIGEST, supra note 7, at 84.
86. Id.
considered "generally recognized as safe." Nonetheless, the agency placed BVO in interim status and requested that new studies on BVO's safety be completed within two and one-half years.\textsuperscript{88} Despite the expiration of this period, FDA maintained the interim status of the additive, on the grounds that studies did "not indicate a reasonable likelihood that a health hazard exists."\textsuperscript{89} This statement, however, misspecifies the required standard of safety. FDA need not show that harm is reasonably likely to occur. On the contrary, the agency must be convinced that harmlessness is reasonably certain. As of 1977, the interim regulation of BVO remained in effect.\textsuperscript{90}

Saccharin is another substance that was placed on interim status when evidence of harm warranted its disapproval. The National Academy of Sciences, responding to studies suggesting the carcinogenicity of saccharin, issued a report in 1970 stating that "the available toxicity studies on saccharin were inadequate to evaluate its carcinogenic potential" and recommended further studies.\textsuperscript{91} Thus, reasonable certainty of harmlessness did not exist in 1970.

FDA issued an interim regulation for saccharin in 1972, noting that the long-term studies recommended by the Academy were in progress and had thus far indicated "possible adverse effects."\textsuperscript{92} A year later, FDA extended the interim status of saccharin and at the same time identified a number of studies showing a statistically significant incidence of bladder tumors in the male offspring of rats fed the sweetener.\textsuperscript{93} In 1976, the Director of the Division of Pathology in FDA's Bureau of Foods stated that "dose-related carcinogenicity" had been "clearly established" for bladder tumors in rats.\textsuperscript{94} Only in March, 1977, after Canadian tests conclusively demonstrated the carcinogenicity of saccharin in animals, did FDA propose to withdraw its approval as a food additive.\textsuperscript{95}

It is difficult to see how the evidence available before March, 1977, could have been rationalized as consistent with the statutory standard. It


\textsuperscript{90} Brominated Vegetable Oil, 21 C.F.R. § 180.30 (1977).

\textsuperscript{91} National Academy of Sciences, The Safety of Saccharin for Use in Foods (1970).

\textsuperscript{92} 37 Fed. Reg. 2437 (1972).

\textsuperscript{93} Safety Questions on Saccharin, supra note 82, at 8-9.

\textsuperscript{94} Id. at 9.

appears that FDA was judging the evidence of risk from saccharin use against a distorted version of the standard. In 1974, the FDA Commissioner justified the continued interim status of saccharin on the grounds that there were no data "that are persuasive . . . that [saccharin] is clearly a carcinogen."96 But clear proof of carcinogenicity is not required to remove an additive; a credible suspicion of its carcinogenicity would be sufficient to violate the standard.97

b. Interim status for color additives of questionable safety

While FDA has not formally established an interim status for color additives, it has permitted the continued marketing of color additives for which it has acknowledged substantial questions of safety and mandated additional testing.98 For example, serious questions have arisen concerning the safety of Red Dye No. 40, one of the principal replacements for Red Dye No. 2, which was banned in January, 1976.99 A working group appointed by FDA to evaluate the scientific studies on Red Dye No. 40 concluded "that the experimental data to date suggest . . . an association between the incidence or time of appearance of lymphomas or leukemias and exposure to [the dye] in CD-1 mice."100 Nevertheless, FDA decided to await the assessment of "more definitive data" before taking any action against Red Dye No. 40.101 Thus, just as it does with food additives, FDA permits the continued marketing of color additives in the absence of a reasonable certainty of their harmlessness.

c. Interim status for animal drugs of questionable safety

FDA has not formally established regulations governing the general conditions and procedures for interim approval of animal drugs. Nevertheless, FDA has promulgated an interim regulation concerning the use of antibiotics in animals to promote rapid growth.102 These antibiotics were placed on interim status because their use in animals can have a deleterious effect on human health. The use of antibiotics promotes the development of bacterial strains that are resistant to the antibiotics administered. Thus, when antibiotics are given to food-producing animals, there is a risk that resistant strains harmful to humans will be promoted in the animals and passed to

96. FOOD CHEMICAL NEWS, Nov. 4, 1974, at 6.
97. See note 27 supra.
98. The placement of additives that have already been approved on interim status is not to be confused with provisional listing. Provisional listing signifies that full approval has not been granted and applies to color additives that had been used commercially in or before 1960 but had not been adequately tested for safety. See note 42 supra.
101. Id.
human beings by the ingestion of food from treated animals. Antibiotic treatments to eliminate the resulting disease in human beings will not be fully effective against the resistant strains.\textsuperscript{103}

To justify the continued approval of these uses of the antibiotics, FDA again espoused a broad interpretation of the reasonable certainty of harmlessness standard. FDA noted that a task force of scientists selected by the agency had arrived at "the logical conclusion, though not fully documented, that [the non-therapeutic uses of antibiotics] give rise to a human health hazard."\textsuperscript{104} The agency acknowledged that "every expert committee that has reviewed this issue has concluded in general terms that a potential or theoretical human health hazard exists."\textsuperscript{105} Nonetheless, FDA permits their continued use. In arriving at its decision, FDA overtly adopted a relative safety standard:

The concept of 'safety' as used in this act does not require complete certainty of the absolute harmlessness of a drug, but rather the reasonable certainty in the minds of competent scientists that it is not harmful, \textit{when balanced against the benefits to be obtained from the drug}.\textsuperscript{106}

However, as has been shown above, the Animal Drug Amendments authorize no such balancing of risks and benefits.\textsuperscript{107} As it has for food and color additives, FDA has diverged from the safety standard Congress established.

3. \textit{Interpretations Relating to Previously Approved Additives—Full Approval for Additives of Questionable Safety}

In some cases, FDA has not even placed food additives of newly questionable safety on interim status, but has used a relative safety standard to justify the continued full approval of such additives long after the appearance of serious doubts about their safety. Nitrates and nitrites, which are used primarily in cured meats as preservatives, colorants, and flavorizers, are in this category of food additives.\textsuperscript{108} When nitrates and nitrites come in contact with certain naturally occurring amines found in the human stomach, they may form nitrosamines, a large class of chemicals some of whose members are known carcinogens.\textsuperscript{109} Despite this possibility, FDA refused in 1972 to withdraw its approval of nitrates and nitrites because it judged the "risk of the possibility of a chronic illness (cancer)" to be outweighed by "a very real and more immediate hazard (botulism)" which

\textsuperscript{104} \textit{Id.}
\textsuperscript{106} \textit{Id.} at 9812 (emphasis added).
\textsuperscript{107} See text accompanying notes 45-54 \textit{supra}.
\textsuperscript{109} \textit{Id.} For additional discussion of the hazards of these chemicals, see M. Jacobson,
the additives prevent. In September, 1977, FDA seriously raised the possibility of either withdrawing approval for the use of nitrates and nitrites in poultry products or placing such uses on interim status. The agency still based its reluctance to remove these additives from the market on their purported benefits.

This balancing might be desirable if there were no other means to avoid botulism, and if FDA were actually selecting the means to minimize overall harm to consumers. However, FDA poses a false dilemma; it is not necessary to choose between the threat of botulism and the threat of cancer. The meats can be preserved in other ways. Moreover, even if the meats could not be made available safely without these additives, there are substitute foods available. Because the physiological advantages of substitute foods or alternative means for producing and preserving foods are always available, the problem does not involve a necessary trade-off of physiological benefits and risks.

4. Summary of FDA's Interpretation of the Statutory Standard

FDA regulations governing new approvals, with the exception of those for color additives, present an ambiguous interpretation of the safety standard and have been applied so as to permit approval of additives for which serious questions of safety exist. With regard to additives previously approved, FDA implicitly establishes a relative safety standard through its device of interim regulations. Moreover, in practice, FDA permits continued marketing of additives of potential or known harm.

B. Interpretations by the Courts

The courts have not given extensive attention to the standard applied to the approval of additives. There have been few opinions discussing the standard and, even among these opinions, the discussion has been limited largely to dicta. The tenor of the courts' comments suggest that the courts have done no better than FDA in comprehending the standard of safety established by Congress for additives.

How Sodium Nitrite Can Affect Your Health (Center for Science in the Public Interest, Washington, D.C. 1973) [hereinafter cited as M. Jacobson, Sodium Nitrite]; V. Packard, supra note 7, at 111-18; J. Verrett & J. Carper, supra note 7, at 141-47. There is, however, some dispute about whether the hazard has been well established, and some commentators advocate further studies of the problem. See Wolff & Wasserman, Nitrates, Nitrites, and Nitrosamines, 177 Science 15 (1972).

110. Use of Sodium Nitrite, Sodium Nitrate, Potassium Nitrite, and Potassium Nitrate, 37 Fed. Reg. 23,456 (1972). The FDA Commissioner did propose to amend the food additive regulations to withdraw approval of nitrates and nitrites for a few "non-essential" uses. These limited "non-essential" uses of nitrates and nitrites included, for example, the use of sodium nitrite in canned pet food containing meat or fish. In any case, none of the regulations was finally promulgated.


112. Id. at 44,380.

113. "While nitrite is one effective inhibitor of botulinum, refrigeration, freezing, and
In *Jacobson v. Edwards*, a 1971 decision of the district court for the District of Columbia, the court upheld FDA's interim regulation governing BVO. Without defining the specific content of the safety standard, or discussing the evidence on the safety *vel non* of BVO, the court concluded that reasonable certainty of harmlessness existed for the additive. The opinion, therefore, does not illuminate the court's interpretation of the safety standard or the reasons why the interim regulation was considered consistent with the reasonable certainty of harmlessness standard.

In *Continental Chemiste Corporation v. Ruckelshaus*, a 1972 case involving the regulation of a pesticide by the Environmental Protection Agency, the Seventh Circuit Court of Appeals characterized the safety standard for food additives as a relative safety standard. The court stated:

The test of safety was intended to take into account the broader concepts of safety under the intended conditions of use; the benefits of the additive were to be evaluated rather than merely its potential for harm.

In addition, the court asserted that the standard for food additives was the same kind of substantive standard of product safety as that applicable to pesticides, which the court had recognized earlier in its opinion as a relative safety standard.

The court's interpretation of the safety standard is based on two statements in the Senate report on the Food Additives Amendment which the court incorrectly took to authorize the balancing of benefits and risks. The first passage states:

[A] flaw in existing law which has proved detrimental to consumers, to processors, and to our national economy and which this bill seeks to remove is a provision which has inadvertently served to unnecessarily proscribe the use of additives that could enable the housewife to safely keep food longer, the processor to make it more tasteful and appetizing, and the Nation to make use of advances in technology calculated to increase and improve our food sup-

sterilization are also effective and, indeed, are widely used by the meat industry to prevent spoilage.” M. Jacobson, Sodium Nitrite, *supra* note 109, at 31.


115. The court based its decision on two alternative grounds. The ground discussed in the text is the one relevant to this Article. The other ground for decision was jurisdictional; the court concluded that a challenge to a food additive regulation should have been brought in the court of appeals.

116. 461 F.2d 331, 4 ERC 1181 (7th Cir. 1972).

117. *Id.* at 340, 4 ERC at 1188 (citations omitted).

118. *Id.*

119. The court had stated:

The substantive standards [for pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act], phrased in terms of protection of the public and impact on living man, require consideration of the aggregate effect of a product's use upon the environment, including not only its potential for harm, but also the benefits which would be lost by removing it from the market.

*Id.* at 335-36, 4 ERC at 1184-85.
plies. . . . [E]xisting law should be changed to permit the use of such additives as our technological scientists may produce and which may benefit our people and our economy when the proposed usages of such additives are in amounts accepted by the Food and Drug Administration as safe. . . . The concept of safety used throughout this bill centers on the question of whether a substance is safe for use with reference to the health of man or animal.\textsuperscript{120}

This statement merely indicates that Congress intended to revise an earlier standard that had forbidden marketing of substances that are deleterious at high levels of use, even if safe under proposed conditions of use. However, the fact that Congress rejected this earlier approach in favor of a test for safety under the proposed conditions of use does not mean that Congress adopted a relative safety standard; it is possible to establish a reasonable certainty of harmlessness at low levels of use even where a substance is harmful at higher levels of use.\textsuperscript{121}

In construing the statutory standard as a relative safety standard, the court also relied upon a statement in the Senate report that the bill would make possible the use of additives discovered by our scientists which, having been adjudged safe for humans and animals when used in or within certain quantitative limits, could materially advance our ability to make more wholesome foods available to more people at all seasons and, perhaps, we hope, to assure ourselves and others the ability to stockpile supplies of healthful and appetizing foods over such long periods of time as emergencies might make either desirable or essential.\textsuperscript{122}

This statement merely reflects an optimism about the results of using additives that are approved as safe under proposed conditions of use. It does not reveal an intent to balance benefits against risks in determining whether an additive is safe.

In \textit{Hess and Clark v. FDA},\textsuperscript{123} a 1974 case dealing with use of the drug diethylstilbestrol (DES) in cattle,\textsuperscript{124} the District of Columbia Circuit Court of Appeals reversed the decision of FDA\textsuperscript{125} to withdraw summarily FDA approval of the drug. The decision that a summary withdrawal of approval

\textsuperscript{120} S. REP. No. 2422, 85th Cong., 2d Sess. 2 (1958), \textit{reprinted in LEG. RECORD}, supra note 14, at 60, \textit{quoted at} 461 F.2d 340 n.35, 4 ERC 1188 n.35.

\textsuperscript{121} For a suggestion that a reasonable certainty of harmlessness for carcinogens cannot be shown to exist at any level of use, see note 36 supra.

\textsuperscript{122} S. REP. No. 2422, 85th Cong., 2d Sess. 3 (1958), \textit{reprinted in LEG. RECORD}, supra note 14, at 61, \textit{quoted at} 461 F.2d 340 n.36, 4 ERC 1188 n.36.

\textsuperscript{123} 495 F.2d 975, 4 ELR 20,147 (D.C. Cir. 1974).

\textsuperscript{124} DES is a synthetic estrogen known to cause human cancers. When administered to cattle either as a feed additive or as an implant in the animal, it increases the efficiency of the animal's conversion of feed to protein. Epstein, \textit{Pollution and Health}, in \textit{The New Genetics and The Future of Man} 179, 197-98 (M. Hamilton ed. 1971). For a discussion of its carcinogenicity, see H. WELLMAN, \textit{Sowing the Wind} 157-69 (1972).

was not appropriate rested on two grounds not relevant here. However, in
the course of exploring what FDA must show on remand to support a
withdrawal, the court incorrectly embraced a relative safety standard. The
court stated:

[T]he typical issue for the FDA is not the absolute safety of a drug.
Most drugs are unsafe in some degree. Rather, the issue for the FDA
is whether to allow the sale of their drug, usually under specific
restrictions. Resolution of this issue inevitably means calculating
whether the benefits which the drug produces outweigh the costs of
its restricted use. . . .

Thus, as to the relationship of the [DES] residues and safety,
there exists in this case at least three issues: . . . (3) whether, if the
residues are harmful, the FDA should keep DES implants from the
market, in light of their acknowledged value and of the possibility
for meaningful restrictions [other than a ban] on consumption of the
residues.

The court cited no statutory provisions or legislative history to support this
view of the Animal Drug Amendments. It relied only on an article by
Richard Merrill, formerly FDA’s General Counsel, paraphrasing George
Larrick, a former FDA Commissioner, which stated that relative safety is
the standard for drug approvals. But both Larrick and Merrill were
referring to the safety standard governing human drugs, which are con-
trolled by other statutory provisions, and for which Congress had intended
to establish a relative safety standard. However, as has been shown

126. The grounds were: (1) FDA’s failure to give DES manufacturers adequate notice of
its intention to withdraw the drug’s approval, 495 F.2d at 982-88, 4 ELR at 20,148-53; and (2)
the presentation of substantial material issues of fact by the plaintiffs concerning the validity of
FDA’s testing method and the safety of the DES residues detected by FDA. Id. at 992-93, 4
ELR at 20,156. For reasons not relevant to this discussion, FDA’s decision was not based on
the Delaney Clause, but on the generally applicable safety provisions. Id. at 991, 4 ELR at
20,150.

127. Id. at 993-94, 4 ELR at 20,157 (citations omitted). See also Chemetron Corp. v.
United States Dep’t of Health, Education & Welfare, 495 F.2d 995, 4 ELR 20,158 (D.C. Cir.
1974) (discussing the same issue; decided on the same day and on the same grounds as Hess).
This opinion does not offer additional doctrine, but one passage emphasizes the strong influ-
ence of the purported benefits of DES had on the court:

[DES] enables [cattle] to grow faster while using less feed, and while generating less
solid waste. When used in this fashion, DES yields significant economic benefits for
beef consumers.

Counter-balancing these benefits is a known risk: DES is a carcinogen. . . .

128. Id. at 994 nn.59 & 60, 4 ELR at 20,157 nn.59 & 60 (citing Merrill, Compensation for
Prescription Drug Injuries, 59 Va. L. Rev. 1, 9-12 (1973)).

129. Larrick’s statements were made in 1964, before the 1968 Animal Drug Amendments
were enacted. He was referring to the process for approving drugs under the 1962 New Drug
Amendments, in which Congress established a relative safety standard. While animal drugs
were subject to these provisions before 1968, they were also subject to the Food Additives
Amendment if they could be expected to be present in food. Such drugs had to meet the more
rigorous safety test for food additives. See note 54 supra. In any event, after separate
above, \(^{(130)}\) the safety standard governing animal drugs is equivalent not to the standard for human drugs, but to the standard for food and color additives. \(^{(131)}\)

As mentioned above, these discussions reflect only dicta. The meaning of the safety standard should be regarded essentially as a question of first impression for the courts. \(^{(132)}\)

**C. Legal and Regulatory Implications of Current Interpretations of the Standard**

The preceding account suggests that both FDA and the courts have misinterpreted the standard of safety applied to additives. This misinterpretation has significant consequences for the coherence and effectiveness of the regulatory process. By breaching the statutory reasonable certainty of harmlessness standard while maintaining that it is upheld, FDA creates confusion, weakens its credibility, and establishes a poor foundation for provisions for animal drugs were enacted in 1968, whatever relevance Merrill and Larrick’s statements may have had to DES was lost.

\(^{(130)}\) See text accompanying notes 45-54 supra.

\(^{(131)}\) In the subsequent proceedings over DES, manufacturers urged FDA to consider the benefits of the chemical. Without use of the drug, the annual per capita increase in the cost to consumers of beef was estimated at $2 to $3, yielding approximately $503 million in aggregate cost increases to consumers. Diethylstilbestrol: Notice of Opportunity for Hearing or Proposal to Withdraw Approval of New Animal Drug Applications, 41 Fed. Reg. 1804, 1807 (1976). FDA, however, refused to concede the propriety of taking economic benefits into account.

The Commissioner notes that the economic importance of diethylstilbestrol to a particular industry or even its effect on consumer beef prices is not relevant to or determinative of the acceptability of detection methods offered to justify exception of the drug from the anti-cancer clause, nor is it relevant to the safety of residues resulting from the use of the drug.


\(^{(132)}\) While under some circumstances, administrative and judicial interpretations of a statute may override the original congressional intent, these circumstances are not present regarding the approval of additives. Administrative or judicial interpretations that differ from the original meaning intended by Congress may be upheld where Congress re-enacts the law in question, and: (1) there is clear evidence of congressional intent to re-interpret the statute, cf. Freeman v. Chicago Title & Trust Co., 505 F.2d 527 (7th Cir. 1974) (amendment of statute, following divergent judicial interpretations of the original statute, to reinforce the original congressional intent); or (2) the divergent interpretation clearly has been brought to the attention of Congress before re-enactment. Thompson v. Clifford, 408 F.2d 154 (D.C. Cir. 1968).

With respect to the safety standard for additives, there have been no enactments since passage of the Animal Drug Amendments in 1968. No judicial opinions on the subject pre-date the 1971 Jacobson decision. The administrative interpretations that diverge from the standard do not pre-date 1971. See text accompanying notes 51-53 supra. Even if such interpretations existed before the passage of the 1958, 1960, and 1968 Amendments, the legislative histories of these Amendments show no intent to adopt such interpretations.

Congressional ratification of particular administrative regulations may also be inferred in some cases where Congress has continued to make particular appropriations.

But ratification by appropriation, no less than ratification by acquiescence requires affirmative evidence that Congress actually knew of the administrative policy. . . . Moreover, to constitute ratification, an appropriation must plainly show a purpose to bestow the precise authority which is claimed.

Thompson v. Clifford, 408 F.2d 154, 166 (D.C. Cir. 1968). Where Congress has merely continued appropriations for additive regulation, no such plain purpose can be found.
regulation. Furthermore, these misinterpretations not only erode the reasonable certainty of no harm standard when serious questions of safety arise relating to approved additives, but also threaten to erode the standard at all other points in the regulatory process.

FDA's action provides the basis for applying the weaker standard to new approvals. Such an erosion in the standard of approval for new food additives has already occurred, as indicated earlier, with regard to plastic bottles containing carbonated beverages.133

As to already-marketed additives for which substantial questions of safety have been raised, the weakening of the safety standard encourages delay in the resolution of serious safety questions. The purported compliance by FDA with the reasonable certainty of no harm standard, even after substantial questions of safety have been raised, creates positive incentives for industry to postpone research that might demonstrate a product's harmfulness and result in its withdrawal.134

The misspecification of the standard of safety also has implications for litigation over the withdrawal of additives. For example, it may affect the prerequisites for administrative adjudication on the withdrawal of an additive's approval. Before withdrawing approval of an additive, FDA must provide sufficient notice and an opportunity for a hearing when a material question of fact has been raised.135 In order to withdraw an additive from the market under the standard of safety established above, FDA needs only to show that a question of safety that violates the standard has arisen. Rather than being required to rely on studies that demonstrate conclusively the harmfulness of an additive, FDA may rely on evidence that, because of

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133. See text accompanying notes 64-72 supra.
134. The interim regulation of BVO presents a vivid example of how the confusion over the concept of safety encourages delay in the resolution of safety questions. Although FDA officially recognized questions of safety with regard to BVO in 1970, and requested studies to be completed within two and one-half years, as of the end of 1977 FDA permitted continued marketing of the substance even though safety questions had not been resolved. See text accompanying notes 87-90 supra.

Industry is not always required to undertake the scientific studies necessary to resolve safety questions. Sometimes FDA selects research organizations to undertake such studies. See Saccharin and its Salts, 38 Fed. Reg. 13,733 (1973) (research on saccharin under contract to National Academy of Sciences—National Research Council). But even in these cases, an "accurate" characterization of the safety status of an additive would encourage industry to contribute to a resolution of safety questions.

135. 21 U.S.C. § 348(h) (1970) (food additives); id. § 376(d) (color additives); id. § 360b(e)(1) (animal drugs).
imperfections in methodology or other inadequacies, only suggests rather than establishes the harmfulness of an additive. Accordingly, in order to obtain a hearing, a manufacturer or proponent of use must demonstrate that the new evidence on which FDA bases its notice of withdrawal may not create a question of safety serious enough to violate the statutory standard. This "burden" cannot be met by calling attention to imperfections in the evidence on which FDA relies. A manufacturer must demonstrate inadequacies in the studies so substantial that the studies no longer raise a question of safety serious enough to violate the standard. Because FDA is only required to show the existence of a serious question of safety in order to withdraw approval of an animal drug, FDA need only show conclusively that such a question of safety exists in order to deny a hearing.136

There are additional ways in which confusion about the safety standard may affect litigation. In any attempt by FDA to withdraw approval of an additive because it violates the reasonable certainty of no harm standard, FDA's stretching of the reasonable certainty standard or assertion of identity between the reasonable certainty and relative safety standards could backfire. Industry could cite the agency's own interpretations against it in order to persuade the courts that the proper safety standard would allow additives to be marketed so long as there was no reasonable likelihood of their harmfulness or so long as purported benefits exceed risks. The courts have already shown themselves open to such reasoning.137

In addition, because a relative safety standard involves not only questions of safety, but also questions concerning the appropriate trade-off between the benefits and risks presented by the use of a substance, decisions

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136. The appropriateness of summary withdrawal in administrative adjudication over additives has been dealt with only in one case, Hess and Clark v. FDA, 495 F.2d 975, 4 ELR 20,147 (D.C. Cir. 1974), discussed in the text accompanying notes 123-131 supra. In Hess, the court found FDA's attempt to withdraw approval of the animal drug DES through summary proceedings invalid, in part because petitioners had raised "material issues" over the detection of DES in animal carcasses. Here, our discussion addresses only the validity of summary withdrawal proceedings where questions are raised as to the harmlessness of an additive, and does not treat the relative burdens concerning the detection of deleterious substances. It could be argued, however, that with regard to animal drugs the same kind of analysis and justification applied to questions of harmlessness in summary withdrawal proceedings are applicable to questions of detection. In the case of animal drugs, the manufacturer has the burden of demonstrating the safety of the animal drug. This involves a consideration of "the probable consumption of such drug and of any substance found in or on food because of the use of such drug." 21 U.S.C. § 510(d)(2) (1970). Thus the presence and level of the drug in animal carcasses are elements of the required showing of safety. It could be argued that if the proper interpretation of the safety standard permits FDA to proceed by summary procedures when it has merely shown the existence of a question concerning the harmfulness of the drug, so too it may proceed summarily when it has a question concerning the presence of an animal drug, such as DES, in animal carcasses. Therefore, under this interpretation, the mere fact that the manufacturer in Hess raised questions concerning the detection of DES in food should not necessarily assure it the right to a hearing. The manufacturer's right to a hearing would depend on whether the evidence they offered was strong enough to undermine the serious possibility that DES had been detected in animal carcasses.

137. See text accompanying notes 116-131 supra.
by FDA to withdraw additives under a relative standard are more difficult to sustain than those made under the statutory standard. Where evidence of harm is solid, a manufacturer might contest a decision under a relative safety standard by dramatizing the benefits of a substance.

III
THE CASE FOR THE REASONABLE CERTAINTY OF HARMLESSNESS SAFETY STANDARD

To this point, this Article has assumed the desirability of excluding the consideration of benefits from additive regulation. Obviously, this assumption is not universally accepted. Many commentators on additive regulation, and on health and environmental regulation in general, believe that a relative safety standard, allowing case-by-case balancing of benefits and risks, leads to better outcomes. The record of FDA regulation and judicial decisions shows a tendency to drift towards this view. There would be no point in forcing FDA to adhere to the former standard if the latter were in fact more desirable; it would be better to change the statutory standard or ignore violations of an unwise standard. However, strong arguments can be made that the mix of safety and the benefits of modern food technology resulting from the regulatory scheme established by Congress is superior to the mix that would result from a system of case-by-case judgments based on risks and benefits.

In order to apply correctly a risk-benefit standard, the regulatory authority must be capable of establishing quantifiable measures of: (1) the net social benefit that may be derived from the use of a particular additive; (2) the incidence of physiological risks that attend the use of the additive; and (3) the terms on which the public would consider additional risks.


Several commentators on additives in particular have assumed both the authority for this kind of analysis and the wisdom of it. For example, Gerald B. Guest, Special Assistant to the Director of FDA’s Bureau of Veterinary Medicine, has written:

The trend toward more demands in efficacy and safety considerations will have, in my judgment, a beneficial effect on benefit-risk analysis. The more precisely we document the efficacy and the more thoroughly we pursue safety questions, the better position we are in to make true benefit-risk oriented decisions.

Guest, Use of Drugs in Feeds, 29 FOOD DRUG COSM. L.J. 50, 54 (1974). James Turner, an attorney specializing in food law, has written:

Unlike the color additive amendments, the food additive amendments address a class of chemicals which includes both important and unimportant additives in the food supply. . . . Therefore the food additives amendment must analyze these various functions to arrive at an accurate assessment of the risk presented by the chemicals versus the benefits they impart.

justified by additional benefits (the social risk-benefit preference function). The authority must also have resources adequate for carrying out the requisite economic and physiological analyses. In addition, an optimum regulatory outcome depends on the authority’s neutrality. The authority’s decision should be influenced solely by the risk-benefit calculus, and not disproportionately by views pressed by special or political interests.

In the real world, the regulatory authority is neither omniscient nor neutral. It has problems in meeting all of the requirements for the conduct of risk-benefit analysis.

A. Difficulties in Estimating Benefits

The overall social benefits of an additive are the net result of the effects of its use on all producers and on the public. However, to date, the immediate benefits to food processors stemming from use of an additive have been used as the primary measure of the additive’s overall benefits. For a number of reasons, benefits to food processors are a misleading, if not inaccurate indicator of overall social benefits.

First, the current cost advantages related to the use of an additive are a short-term measure of benefits and may not reflect the positive effects the withdrawal of an additive might have upon future prices of existing substitutes. In addition, the rise in production costs caused by the withdrawal of an additive may stimulate research into new techniques of production and encourage development of new and safer alternatives. In the long run, the effects on processors caused by withdrawal of an additive are likely to be far less than those suggested by the current cost savings related to its use.

Second, because overall social benefits are the net result of effects on all producers and the public, measuring benefits by the gains in market share of a single processor resulting from the use of a new flavorizer or colorant may also be misleading. The gains of a particular producer in market share may be offset by losses in the market shares of other producers and thus result in no net benefit to producers as a class.

Third, even when additives do reduce costs to processors, lower costs may not be passed on in lower prices. This is because of the oligopolistic nature of the food processing industry, which is characterized by large firms, and the existence of highly concentrated markets and high barriers

139. For example, there is—according to one analyst—six cents worth of saccharin in a gallon of syrup concentrate, compared with one dollar’s worth of sugar in a gallon of regular concentrate, with little difference in price. Impact of Saccharin Ban on Soft-Drink Firms Likely to Be More Adverse than seen at First, WALL ST. J., Apr. 27, 1977, at 39, col. 3.

140. In 1964, the 100 largest food processors each held four or more of the top eight positions in 70% of the 116 food product classes. NATIONAL COMMISSION ON FOOD MARKETING, THE STRUCTURE OF FOOD MANUFACTURING: A REPORT BY THE STAFF OF THE FEDERAL TRADE COMMISSION 5 (Technical Study No. 8, 1966).

141. In 1963, the market share accounted for by the top four firms varied from under 25% for such product classes as animal feed, butter and margarine, pickles, and fish, to over 85% for
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to the entry of new firms.\textsuperscript{142} Industries with these characteristics may be expected to be insensitive to the full rigors of price competition. Competition between such firms involves product variation, advertising, and other elements of non-price competition, all of which involve additional costs.\textsuperscript{143} Thus, rather than resulting in lower product prices, any reduction in costs of production brought about by the use of an additive may be absorbed in increased advertising, promotion, packaging, and other means of non-price competition. These elements of performance appear to apply to the food manufacturing industries.\textsuperscript{144}

The use of additives particularly encourages superficial product differentiation, an important means of competition in the food industry.\textsuperscript{145} Many additives, such as artificial flavors and colorants, are used to differentiate virtually identical foodstuffs from one another. Preservatives, stabilizers, thickening agents, and other additives permit production of a single basic food in many trivially different forms. Superficial product differentiation, whether brought about by advertising, packaging, or the use of additives, adds little to social welfare at best. Each processor spends heavily on differentiation in an attempt to improve its market share at the expense of another or to defend its share against such attempts by another. The expenditures merely influence the distribution of sales and profits within the industry. They do not give consumers commensurate benefits, and thus represent wasted resources.\textsuperscript{146}

In addition to encouraging superficial product differentiation, some new additives may contribute to market concentration in additional ways. For example, additives that increase the longevity of products allow marketing of such products on a national basis. This makes possible national television and other mass media advertising campaigns which are not efficient on a local basis, contributing to market concentration on a national level.\textsuperscript{147}

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\textsuperscript{142} See B. IMEL, M. BEHR, & P. HEMELBERGER, \textit{Market Structure and Performance: The U.S. Food Processing Industries} 90-93 (1972). Over half the classes had four-firm concentration ratios over 50%.\textit{See id.} In 1964, the 50 largest food manufacturers accounted for 61% of total profits, about 65% of all food advertising expenditures, and over 50% of total industry assets. \textit{National Commission on Food Marketing, supra} note 140, at 214.

\textsuperscript{143} \textit{See National Commission on Food Marketing, supra} note 140, at 213-17.

\textsuperscript{144} For a general treatment of oligopolistic performance, see J. BAIN, \textit{Industrial Organization} (1968).

\textsuperscript{145} \textit{National Commission on Food Marketing, supra} note 140, at 215-16.

\textsuperscript{146} Product differentiation creates a need for, and in turn is spawned by, advertising. In 1965, food manufacturers—the largest users of television advertising—accounted for more than 20% of all advertising expenditures by United States manufacturing companies. \textit{Id.} at 215.


\textsuperscript{146} The role of additives in contributing to oligopoly in the food processing industry is...
Another factor to subtract from the apparent benefits of additives is their negative effect on nutrition. Some new products made possible by additives contain little protein, minerals, or vitamins, but consist mainly of carbohydrates, fat, water, and additives. Many such foods—such as candy, soft drinks, potato chips, cookies, and crackers—provide little or no essential nourishment. To the extent that they displace basic foods in the diets of children, they may cause physical underdevelopment. While the statute does not authorize FDA to keep an additive from the market on the basis of this indirect contribution to ill health, this consideration is relevant to an assessment of the real benefits of additives.

Thus, a full analysis of additive benefits cannot be limited to a simple enumeration of the immediate private benefits of their use. The analysis must subtract from these apparent benefits the economic waste associated with superficial product differentiation, advertising, and other forms of non-price competition. It must consider the possibility that real cost savings from additives do not reach consumers. Finally, it must subtract from benefits the contribution of additives to poor nutrition.

**B. Difficulties in Estimating Risks**

The risks of additives are also difficult to estimate. In contrast with benefits, however, risk estimates tend to underplay the real incidence of harms from toxic substances.

Some additives have been linked to such short-term harms as acute allergic reactions and miscarriages. Other additives may cause long-term harms such as: cancer of the stomach, lungs, breast, skin, bladder, liver, and blood system; birth defects and mutations; damage to the heart, liver, kidney, thyroid, and central nervous system; and various behavioral disabilities.

Information on potential hazards is incomplete and uncertain. The tools for discovering the existence of risks are imperfect. Direct resort to epidemiological data on human experience is limited by the length of the periods required to reveal the slow cumulative effects of toxic substances.

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The difficulties in using human data are increased by problems in disentangling the effects of an additive from the effects of the numerous other additives, pollutants, and other environmental factors affecting the target population. Consequently, most toxicological information is obtained from animal studies. For a number of reasons, this methodology necessarily creates a high level of uncertainty about the additive's physiological effects on humans. First, the tests use a number of genetically pure strains of test animals (typically mice, rats, hamsters, or rabbits) in an attempt to determine correlative effects on all human races and conditions. Second, the test animals are often inherently less sensitive to many chemicals than human beings. For example, with respect to thalidomide, human beings are from thirty to two hundred times more sensitive than rabbits, mice, rats, hamsters, and dogs. Third, test animals are maintained under ideal conditions and, unlike human beings, are not subjected to numerous additives, pollutants, debilitating diseases, and stress. The animal studies do not provide information as to the extent to which these various factors may act synergistically to create or reinforce the impact of any additive. Fourth, animal studies are able to reveal only those physical effects readily observable by pathologists and those mental impairments that are revealed by the epidemiological studies on saccharin illustrate the difficulty of establishing toxic relationships through such studies. Four studies conducted in recent years failed to find a causal relationship between saccharin and human bladder cancer. See Burbank & Fraumeni, Synthetic Sweetener Consumption and Bladder Cancer Trends in the United States, 227 Nature 296 (1970); Armstrong & Doll, Bladder Cancer Mortality in England and Wales in Relation to Cigarette Smoking and Saccharin Consumption, 28 Brit. J. Preventive & Social Med. 233 (1974); Morgan & Jain, Bladder Cancer: Smoking, Beverages and Artificial Sweeteners, 111 Can. Med. A.J. 1067 (1974); Kessler, Non-Nutritive Sweeteners and Human Bladder Cancer: Preliminary Findings, 115 J. Urology 143 (1976).

Canadian researchers did not demonstrate a relationship between cancer and saccharin in human males until 1977. N.Y. Times, June 18, 1977, at 8, col. 1. The earlier studies all suffered from serious limitations. For example, if the latency period were longer than five years, the study by Burbank and Fraumeni could not have detected the relationship. Detection of the relationship is difficult even for studies surveying a longer period, such as that by Armstrong and Doll. This is because increased public consumption of saccharin is a relatively recent phenomenon, and thus, the number of people long exposed to large amounts of saccharin is small.

The reports by Kessler and by Morgan and Jain involve studies of only a few hundred bladder cancer patients and members of control groups. Such studies are unlikely to detect a causal relationship unless saccharin is responsible for a major percentage of bladder cancer from all sources. Finally, as all these studies concentrate on cancer of the bladder, they would not reveal any effect saccharin might have had on other organs.

152. Id. at 29.
153. For a general description of testing methods and an appraisal of their limitations, see J. VERRETT & J. CARPER, supra note 7, at 51-65; M. JACOBSON, EATER’S DIGEST, supra note 7, at 23-38.
154. 1972 Hearings, supra note 5, at 1105.
155. Id. at 1282 (statement of Samuel Epstein, Case Western Medical School).
156. J. VERRETT & J. CARPER, supra note 7, at 51-53.
physical effects. Finally, these studies have a limited ability to reveal those mutagenic effects that become visible only after several generations, unless multi-generational studies are undertaken. \(^\text{157}\)

The most serious limitation on the validity of animal tests is imposed by restricted budgets and the high costs of testing, which limit the kinds and numbers of animals that can be tested and the range of effects that can be investigated. \(^\text{158}\) The significance of small sample sizes deserves elaboration. Carcinogens, for example, typically affect only a small percentage of an exposed population. In a sample of moderate size, a carcinogen has a good chance of escaping detection altogether. In an experiment using an agent that affects 500 out of 100,000 animals (0.5%), the probability is about sixty percent that no case would appear in a test group of one hundred animals, and the chances are about thirty percent that no case would appear in two such groups. \(^\text{159}\) In partial compensation, high dosages are used in animal tests to increase the rate of response, but experts estimate that all but the most toxic of substances with low probability risks have a good chance of escaping detection. \(^\text{160}\) These low probability risks can lead to a significant number of illnesses and deaths in a population exceeding 200 million.

C. Other Difficulties in Applying a Relative Safety Standard

As shown above, both the benefits and risks of additives are far from straightforward and are clouded in uncertainty. To assess the benefits of additives with known or suspected risks, and to weigh the benefits against the harms requires extensive resources and staff trained in the fields of economics and policy analysis. Even when an agency has the mandate and some of the resources to do such assessments, risk-benefit decisionmaking is a slow process. The Environmental Protection Agency’s experience with the pesticide program illustrates the amount of time and effort which must go into a single regulatory decision. \(^\text{161}\) The low productivity of resources devoted to this use suggests that unless Congress drastically increased FDA’s budget, the agency could make only a few decisions each year and would fall ever farther behind in evaluating additives. \(^\text{162}\)

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157. Id. at 46, 54-57.
158. U.S. COUNCIL ON ENVIRONMENTAL QUALITY, supra note 150, at 29.
159. The proportion of cases in which no cancers would appear is derived from A. WAUGH, LABORATORY MANUAL AND PROBLEMS FOR ELEMENTS OF STATISTICAL METHOD, at Table A22 (2d ed. 1944). For a technical discussion on the probability distribution for low probability events, see R. FISHER, STATISTICAL METHODS FOR RESEARCH WORKERS 57-61 (14th ed. 1970).
160. J. VERRETT & J. CARPER, supra note 7, at 57-65. With relatively small sample sizes, successive tests on a chemical may be expected to disagree on the existence of a low incidence toxic effect. The absence of consistent findings from test to test accounts for the characterization of some additives as involving “substantial questions” of safety and is one reason scientists call for more testing upon finding a suggestion of toxicity in one experiment. Id.
162. See Merrill, supra note 77, at 1005-06.
In practice, FDA neither appears to require extensive evidence on benefits from additive manufacturers nor conducts a searching analysis of the available data. For example, with respect to the four food additives on interim regulation early in 1977—a soft-drink stabilizing agent (BVO),\footnote{21 C.F.R. § 180.30 (1977).} two non-nutritive or low-calorie sweeteners (saccharin\footnote{Id. § 180.37.} and mannitol\footnote{Id. § 180.25.}), and a plastic food container (acrylonitrile copolymer)\footnote{Id. § 180.22.}—FDA described the questions of safety raised at that time, but did not mention the benefits that would justify continued marketing.\footnote{In the notice for a hearing in connection with a proposed withdrawal of approval of DES, FDA mentioned that it had been presented with a rough quantification of some of the costs of withdrawal, but refused to take the benefits into account. See note 131 supra. This case also illustrates the ease of exaggerating the benefits of additive use. Estimates indicated that the withdrawal would cost consumers about $503 million per year in higher beef prices. This figure has been publicized to demonstrate the importance of DES for maintaining the standard of living of the American people. But even if the half-billion dollar figure is accepted as a valid long-run estimate, what Americans are asked by industry to accept is a chance of a significant, but unknown number of additional cases of cancer, in exchange for a short-run saving of about $2.50 per person per annum. Although FDA has recently proposed to take benefits into account in assessing safety, the agency has not committed itself to any “routine formal analysis” of benefits. See note 59 supra. See J. Verrett & J. Carper, supra note 7, at 77-89.}

Even if reliable data on the relevant benefits and risks were obtained in a particular case, there is the further basic difficulty of determining the preferences of the public as to what risks are worth enduring in exchange for what benefits. These preferences are not known, if indeed knowable, by the regulators. Because there is no measure of the public’s value system available for comparison, FDA is not restricted in the weights it can assign to the risk-benefit calculus. There is virtually no level of risk that could not be defended by FDA as appropriate.

A third difficulty that might be encountered in attempting to carry out a relative safety standard is suggested by the inherent bias of the regulatory process. The benefits of additives may be presented as current, pecuniary, evident, and measurable in some degree. The immediate beneficiaries, in many cases relatively few in number, tend to be well-represented before regulatory councils.\footnote{See J. Verrett & J. Carper, supra note 7, at 77-89.} The risks, on the other hand, may be remote in time, dispersed among the population, not necessarily directly evident to bearers, difficult to disentangle from other forces, difficult to quantify, but possibly critical, with bearers minimally represented directly before regulatory councils. Moreover, the complexity of the issues together with the lack of any clearly delineated limit on risk invites full utilization of the persuasive arts of public relations by industry. The result tends toward an unwarranted assumption of risks.
D. The Relative versus Reasonable Certainty of Harmlessness Standards: Conclusions

As discussed above, a real-world regulatory authority would have difficulty administering an appropriate risk-benefit standard.

1. Benefits are difficult to measure because they involve not just the immediate private benefits or cost reductions to some food processors, but the net social effects, including effects on other producers and the public at large.

2. Risk determinations involve a large element of uncertainty because of difficulty in determining the potential effects of consumption on human beings on the basis of limited short-term animal studies.

3. The resource costs for carrying out a case-by-case investigation of relative safety are likely to be extensive, and of doubtful availability.

4. The value system establishing the terms on which risks will be weighed against benefits is unknown.

5. The regulatory authority, subject to biases in sources of information, and unequal advocacy and pressure from the various groups having a special interest in the outcome of regulatory decisionmaking, cannot easily remain neutral or unbiased.

Adoption of either the relative or the reasonable certainty of no harm standard is likely to result in social costs that would not be encountered in an ideal situation, i.e., where the regulators are omniscient and neutral. When FDA employs a relative safety standard for regulatory decisionmaking under the conditions outlined above, the agency is likely to approve the use of additives whose actual risks outweigh their actual net social benefits. On the other hand, the reasonable certainty of harmlessness standard results in a ban on every additive until its safety has been established, thus depriving the public of its net benefits until it is determined to be safe.

It may be argued that the public has more to lose than to gain by applying a relative safety standard to additive approval. The worst possible harm under the reasonable certainty of harmlessness standard involves the sacrifice of net benefits whose average contribution to society, given the products and industries involved, appears to be of no great significance. Moreover, this sacrifice may be only temporary, where the additives in question are later shown to be safe. In the worst possible case under the relative safety standard, preventable harms of a serious and permanent nature may be incurred. By adopting the reasonable certainty of harmlessness standard, Congress has prudently chosen the more cautious approach.

The reasonable certainty of harmlessness standard has another advantage. Society is served by providing incentives to conduct research that reveals what the benefits and risks are. Perhaps the surest way to encourage such research is to induce the potential direct beneficiaries of additives, the
producers of additives and food processors, to bear an increased share of the burden of ignorance by depriving them of the marketing or manufacturing benefits of additives until questions of safety are resolved. This stance puts a greater, but not exclusive burden of regulatory costs on the party that can contribute most effectively to a resolution of the problem. This socially desirable incentive is supported by a reasonable certainty of harmlessness standard. In contrast, the relative safety standard encourages delay by manufacturers in resolving questions of safety, permitting the continued marketing of those additives for which further research may be expected to confirm suspected risks.

There is a yet another advantage to a reasonable certainty of harmlessness standard over the relative safety standard. The knowledge that, under the relative safety standard, products with suspected risks are being approved for marketing would tend to discourage public confidence in the safety of the commercial food supply. This would result in reduced reliance on the commercial food supply by some, in favor of more "do-it-yourself" production of foodstuffs, thus reducing specialization and productivity in food processing activities. The absolute standard, on the other hand, would encourage efficiency and specialization by creating confidence in the commercial food supply.

Thus, a reasonable certainty of harmlessness standard—while not necessarily the optimal standard when applied by an omniscient and neutral regulator—is likely to constitute the superior standard for decisionmaking in the face of limited knowledge and the pressures of the actual world.

IV

REVIVING THE SAFETY STANDARD: RECOMMENDATIONS

On the basis of the above considerations, the preferred standard of safety is the legislative standard adopted in the Food Additives, Color Additive, and Animal Drug Amendments. In accordance with these amendments, the same standard should be established as applicable both to additives newly approved and to those currently on the market. This standard requires reasonable certainty of no harm.

This standard prohibits the marketing of any new additives with known or suspected risks. In addition, the range of scientific tests required to qualify new additives should be broadened and made more explicit. Strict testing at the outset—including, for example, mandatory tests for carcinogenic, teratogenic, and mutagenic effects—would decrease the likelihood that adverse findings would appear in the future, lessening the need for the later withdrawal of approval.

169. For a general statement on this regulatory strategy, see Calabresi, Comments on Preclinical Problems of New Drug Development, in Regulating New Drugs 53-60 (R. Landau ed. 1973).

170. As of 1977, FDA regulations did not require tests for cancer and other low probability
With respect to any additive currently on the market, the legislative standard requires FDA to withdraw approval of an additive once reasonable certainty of harmlessness no longer exists. Statutory sanctions or the threat of their use should be employed to remove an additive from the market in those situations where there develops a reasonable likelihood that an additive is harmful. This stance steers the regulatory outcome toward conformity with the rationale underlying the statutory standard. Further, where FDA could show that it is reasonably likely that an additive is harmful, with solid evidence of risks and no need for additional research and discovery, the agency would have sufficient justification for its action to withstand privately-induced backlash.

Where the risks of harm are not fully established, FDA faces a regulatory dilemma.\footnote{Thig Article recommends that Congress amend the Food, Drug, and Cosmetic Act so as to relieve FDA of this dilemma and induce regulatory action more in line with the statutory goals. This requires specific attention to the processes of removal. First, as is required by current statutory provisions, the amendment should require additives suspected of harm to be characterized as no longer safe. Second, unlike current provisions, the amendment should provide that removal of such additives from the market be delayed for the minimum time necessary to conduct animal studies—two effects. A report of the U.S. General Accounting Office called for mandatory testing of all food additives for carcinogenicity. U.S. General Accounting Office, Federal Efforts to Protect the Public from Cancer-Causing Chemicals Are Not Very Effective, 37 (1976). Dr. Samuel Epstein, a pharmacologist and noted expert on environmental health problems, has written: "Ideally and minimally [additives] should be tested for toxicity per se, carcinogenicity, mutagenicity, and teratogenicity [the capacity to produce birth defects]." Epstein, Pollution and Health, in The New Genetics and the Future of Man 192 (M. Hamilton ed. 1971). 171. See text accompanying notes 73-77 supra.} The statutory standard requires withdrawal of approval not simply when there is a reasonable likelihood that an additive is harmful, but requires such an action whenever the evidence raises any serious question concerning an additive's safety. To find that an additive is no longer safe results in its removal from the market before solid evidence exists that would provide public support for the withdrawal of approval. FDA thus becomes vulnerable to the pressures of the business community, who can make full use of lobbyists, public advertising campaigns, and other instruments of the public relations industry. So to interpret the standard rigorously is to risk reactions that damage the agency's regulatory credibility. The result is either that risks are not officially recognized—even long after evidence of harm has been available—or that the interim regulation device is applied with the effect of giving indefinite sanction to additives that do not meet the statutory standard. In effect, either of these strategies tends to shift the standard from reasonable certainty of no harm to the more permissive standard of allowing the marketing of additives until harm has been demonstrated.

This Article recommends that Congress amend the Food, Drug, and Cosmetic Act so as to relieve FDA of this dilemma and induce regulatory action more in line with the statutory goals. This requires specific attention to the processes of removal. First, as is required by current statutory provisions, the amendment should require additives suspected of harm to be characterized as no longer safe. Second, unlike current provisions, the amendment should provide that removal of such additives from the market be delayed for the minimum time necessary to conduct animal studies—two
to three years. A maximum time limit should be established for delayed removal. During this period, the issues of safety would have to be resolved or the additive would be removed from the market. Third, products containing additives not found to be safe during the period of delayed removal should be required to be labeled as containing substances whose safety has not been established.

This amendment could be expected to have a number of implications for regulatory conduct and the safety of additive use. First, it would encourage manufacturers to resolve questions of safety with greater dispatch. This would be the result of a number of factors: the characterization of additives with suspected risks as no longer safe and the resulting pressures of publicity; the market effects of labeling requirement; and the prospects of mandatory removal after a period geared to the time necessary for research.

Second, a policy of "delayed removal" would help maximize the effectiveness of the statutory standard because it would make feasible the decision to disapprove those additives characterized only by suspected risks. Without the flexibility presented by the option to postpone the ban on unsafe additives, FDA would be tempted to ignore evidence of risks where it was not conclusive. Moreover, information could be generated during the "delayed removal" period that would either exonerate the additive or buttress FDA's case against it.

Third, the labeling requirement would alert consumers to unsuspected risks in the products they buy. Better informed consumers could then make choices that would reflect their individual evaluations of the relative risks and benefits of available goods. Food producers would acquire another dimension of competition; they could emphasize the safety of food ingredients. The impact of risky products could be reduced well in advance of their ultimate removal if consumers, informed of potential hazards, shifted to safer products.

Thus, the option allowing limited delay in removing products not found to be safe would eliminate the pretense—as exemplified by the current use of interim regulations—that an additive is to be considered safe while

172. No extensions would be allowed if the tests were rendered unreliable. This is the position FDA properly took in its decision to withdraw the provisional certification of Red Dye No. 2. See Termination of Provisional Listing and Certification of F.D. & C. Red No. 2, 41 Fed. Reg. 5823 (1976). FDA's position was affirmed by the decision in Certified Color Mfrs. v. Mathews, 543 F.2d 284 (D.C. Cir. 1976). See also Boffey, Color Additives: Botched Experiment Leads to Banning of Red Dye No. 2, 191 SCIENCE 450 (1976).

173. It appears that FDA already has the authority to require such labeling. A food is misbranded, and therefore subject to seizure, "if its labeling is false or misleading in any particular." 21 U.S.C. § 343(a) (1970). Factors to be taken into account in determining whether a label is "misleading" include "the extent to which the labeling fails to reveal facts ... material with respect to consequences which may result from the use of the article to which the labeling relates under the conditions of use prescribed in the labeling thereof or under such conditions of use as are customary or usual." Id. § 321(n). Arguably, that the additive is no longer known to be safe is a material fact.
research is undertaken to determine its safety. By acknowledging that those additives for which serious questions of safety have been raised no longer meet the reasonable certainty of harmlessness standard, FDA would avoid undermining the standard at all points in the regulatory process. This stance would make less onerous FDA's regulatory role in administrative adjudication and before the courts. Further, it would provide fewer incentives for delaying necessary research, and it would thereby strengthen the measures intended by Congress to provide a safe food supply.