
Stretching Delaney Till It Breaks

Richard M. Cooper

THIS PAST JUNE, the Food and Drug Administration (FDA) took steps that effectively overturned more than a quarter century of interpretation of the Delaney clause. For the general understanding of the clause's ruling principle—that no risk is to be accepted from an animal carcinogen deliberately added to the human food supply—the FDA substituted the principle that some risk is acceptable provided it is minimal. Thus the agency drew, depending on your point of view, the sting or the teeth from the most famous public health provision in the U.S. statute books, reducing it to a redundant appendage to the law's general requirements on food safety.

The agency's actions were not a bolt from the blue, nor a dramatic new initiative reflecting distinctive policies of the Reagan administration. Rather, they were a logical (though, as I shall argue, debatable) extension of a series of approaches that the FDA has taken since the early 1970s to specific regulatory problems—sometimes on its own, sometimes under external pressure. Those steps made the agency

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progressively more familiar with quantitative risk assessment, and more confident of its ability to use risk assessment techniques to reach acceptable regulatory decisions. The entire development has a quite interesting internal logic, and is a fascinating historical example of how a profound change in regulatory policy takes place.

The Background

First, some necessary background on the Delaney clause. The Food, Drug, and Cosmetic Act contains three Delaney clauses—one for food additives, another for color additives, and a third for drugs administered to food animals. The gist of each is that a substance—whether food additive, color additive, or animal drug—shall not be deemed safe (and therefore shall not be or remain approved) 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 [such a substance] to induce cancer in man or animal. . . .” Each clause is, in context, a proviso to a general requirement that the substance in question be shown to be “safe.” On the basis of

legislative history, the FDA has interpreted these general safety clauses as requiring “reasonable certainty of no harm” to consumers. “Reasonable certainty” has never been taken to mean zero risk.

The Delaney clauses applicable to animal drugs and animal feed additives contain an important exception. A substance found to induce cancer may nevertheless be used in food-producing animals if the FDA also determines that “no residue of the [substance] will be found (by methods of examination prescribed or approved by [the agency]) . . . in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal.” Thus, one may administer a carcinogenic drug to beef cattle to promote their growth if no residue of it will be found in their meat, and one may administer similar drugs to dairy cows or chickens if no residue of it will be found in their milk or eggs.

The Delaney clause applicable to color additives is divided into two parts. For colorants that people eat, the clause is the same as that for food additives—the additive is to be denied approval if it is found to induce cancer in an animal feeding study or other appropriate study. For noningested color additives, such as cosmetics used on the skin or hair, the rule is different. The law forbids approval if “after tests which are appropriate for the evaluation of the safety of additives for such use or after other relevant exposure of man or animal to such additive, it is found . . . to induce cancer in man or animal.” This language provides a little more flexibility in that it links the appropriateness of a test to the particular uses of a colorant of this kind. A feeding study is thus not *necessarily* appropriate for an externally used color additive.

How Sensitive Must Sensitive Be?

The first problem of regulatory policy arose in implementing the exception for carcinogenic substances administered to food-producing animals. Congress’s thinking appears to have been that if the food that humans eat contains no residue of the substance administered to the animal, then it does not matter that the substance is a carcinogen. The overriding question becomes: is the substance there, in the food?

There is no way to know, of course, unless you look. How hard do you have to look? Congress apparently assumed that you could look hard enough to satisfy yourself, as a scientific matter, that no residue is there. As a matter of

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analytical chemistry, however, you never can look that hard. Every method for detecting residues has some limit to its sensitivity, its capacity to detect. Every method can yield, at best, only a conclusion to the effect that, within the sensitivity of the method, no residue was found. At quantities below the sensitivity of the method, residues may or may not be present. If the statutory exception were interpreted to require methods capable of confirming the total absence of residue, it would be an exception that could never be applied.

The problem of determining how sensitive the analytical methods must be was one that the FDA could not responsibly duck. Presumably, Congress would not have enacted the exception had it not intended that it be reasonably available for use. And Congress expressly provided that exceptions would be implemented by use of analytical “methods . . . prescribed or approved by” the FDA. The natural laws of analytical chemistry notwithstanding, the agency had a clear duty to try to prescribe or approve methods to implement the statutory exception.

How, then, to interpret the exception? In 1973, 1977, and 1979, the agency published *Federal Register* documents grappling with this problem.* Its approach was intended to give the exception a sensible area of application. The approach was very complex and changed over the years, and accordingly I will have to simplify greatly.

*In a revised proposal published in October 1985, it was still grappling.

The FDA's task was to prescribe the sensitivity that analytical methods must have for the agency to be satisfied that a resulting finding of no residue can safely be accepted. To perform that task, the agency turned to quantitative risk assessment. It reasoned that some risks of cancer are so small that we need not be concerned about them. Drawing the line between significant and insignificant risks is, of course, a task fraught with political peril, but the FDA tackled it boldly. It eventually proposed that analytical methods be sensitive enough to detect any residue that, under very conservative assumptions and procedures for quantitative risk assessment, would yield a lifetime risk to humans of one in a million. Below that level, a residue might or might not be present, and the agency would not care.

This proposed solution to a difficult regulatory problem was appealing in its inventiveness, logic, and scientific elegance. Unfortunately,

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ly, it was not made final, in part because of technical problems in the subject matter, but also because its demands on the real world—for dose-response data, for identification of metabolites (successor compounds in the body) and other potential residues, and for the development of analytical methods—appeared to be wildly impractical for most of the products whose manufacturers would invoke the statutory exception. The exercise of developing and refining the proposal, however, had a lasting effect: it acclimated the agency to quantitative risk assessment.

Migrant Additives

The next problem the agency faced was a variation on the theme: It it there? Food additives are of two sorts—direct and indirect. Direct additives are ones that food processors deliberately put into foods to serve a useful purpose—sweeteners, preservatives, emulsi-

fiers, and so on. Indirect additives are ones that serve no useful purpose in food, that processors do not want in food, but that get into food anyway—for example, substances that migrate into food from packaging materials. The statute defines “food additive” to include any packaging material that “may reasonably be expected” to become “a component of” the packaged food.

In 1977, the FDA dealt with soda bottles made from a plastic called acrylonitrile, which the agency concluded, on the basis of an ongoing series of tests, probably caused cancer in rats. In the first design of the bottle that the agency reviewed, under extreme testing conditions there was detectable migration into the soda of acrylonitrile monomer, a residue of the polymerization process used in manufacturing the bottle. The next generation of bottle design, however, produced no migration detectable by a method sensitive to ten parts per billion. Nevertheless, using the data from the study of the first-generation bottle and applying a model of migration, the FDA concluded that migration would occur at a level below the sensitivity of the method. The acrylonitrile monomer was thus “reasonably . . . expected” to become a component of the soda and consequently was an indirect food additive; as such, the FDA could not approve it under the general safety clause applicable to food additives.

To the agency, the policy analysis seemed quite clear. If the acrylonitrile monomer was a food additive, it could not be approved, because it had not been shown to be “safe” and would quite likely be found to induce cancer in animals when tests were complete. That the monomer was a food additive under the statutory definition seemed to follow from the migration analysis. By law the FDA did not have to make any finding of actual nontrivial risk to ban the substance, nor could it take into account the fact that plastic bottles cause fewer accidental injuries than glass ones. The FDA moved to ban the bottles, but it was careful to hold expressly in reserve the legal and policy question whether quantitative risk assessment could ever properly be applied to a carcinogenic food additive.

On judicial review in *Monsanto Co. v. Kennedy* in 1979, the U.S. Court of Appeals for the District of Columbia Circuit, in an opinion by Judge Harold Leventhal, joined by Judges David Bazelon and Spottswood Robinson (none of whom has been known for an antiregulatory

outlook), held that the matter was not so simple:

The Court is . . . concerned, that the Commissioner may have reached his determination in the belief that he was constrained to apply the strictly literal terms of the statute irrespective of the public health and safety considerations. . . . [T]here is latitude inherent in the statutory scheme to avoid literal application of the statutory definition of "food additive" in those *de minimis* situations that, in the informed judgment of the Commissioner, clearly present no public health or safety concerns.

Although the court did not cite the FDA's sensitivity-of-the-method proposal for animal drugs, its concept of a *de minimis* exception is remarkably similar to the agency's solution to the problem of "no residue." In each case, the answer to the question "Is it there?" is reshaped by the application of quantitative risk assessment so as to answer the question, "If it is there, does it present a public health risk?"

In *Monsanto*, however, the analysis advanced a step. Under the sensitivity-of-the-method approach, the FDA would generally not know whether any residue was really present below the level of detection. Under the *de minimis* principle announced in *Monsanto*, the FDA might know that a substance was present but still disregard it. How broadly the *Monsanto* precedent could be applied was tested by succeeding regulatory problems.

More Than Skin Deep: Topical Additives

Another significant step in the progression took place when the agency considered the case of lead acetate, the coloring agent in Grecian Formula hair dye. Feeding studies have found lead to be a carcinogen in animals. Initially, in 1978 and 1979, the FDA nevertheless declined to ban the use of lead acetate in hair dye until it was determined whether the substance is absorbed through the scalp and enters the bloodstream. Combe, Inc., the manufacturer of Grecian Formula, commissioned a radioactive tracer study, which found that a minuscule amount penetrated the skin—one-half microgram per application, compared to a background level of thirty-five micrograms or more in the normal human bloodstream. This in-

crease would have no effect on the steady-state blood level of lead that could be detected by conventional methods of analytical chemistry.

Minute though the effects might be, lead acetate was indeed an animal carcinogen that penetrated the skin and entered the bloodstream. Could it be approved despite the Delaney clause? With a little interpretational inventiveness, the FDA concluded in 1980 that it could be.

Recall that the Delaney clause applicable to color additives has two parts. The first, applicable to ingested color additives, provides that a substance found carcinogenic in an animal feeding study cannot be approved, period. But lead acetate is not ingested, so that part of the Delaney clause did not apply. The second part applies only if the color additive is found to induce cancer in tests "appropriate for the evaluation of the safety of additives for such use"—namely, in this case, use as a hair dye. Here, a finding that a substance caused cancer when fed to animals would be controlling only if the study were found to be "appropriate" for resolving the safety question at issue.

The FDA concluded that the animal feeding studies for lead were not appropriate for evaluating the safety of lead acetate in hair dye, for two reasons. First, the amount of absorption is minuscule, both in absolute terms and in comparison to normal background levels from other sources. Second, quantitative assessments indicated that this small increment posed a lifetime cancer risk well below the level of one in a million proposed by the agency in its earlier *Federal Register* documents on the sensitivity of test methods. In these circumstances, the FDA expressly declined to apply its established policy of declaring that a cancer risk to humans exists when an animal carcinogen is absorbed into the human bloodstream. Thus, it noted:

Advances in the ability of analytical chemists to detect infinitesimally small amounts of substances—such as was [sic] seen by the Combe, Inc. radioactive absorption study on lead acetate—are forcing FDA to confront for the first time the significance of potential risks on the order of those associated with lead acetate hair dyes.

The agency went on to argue that its refusal to apply its established policy toward animal carcinogens was "consistent with both its mandate to protect the public health and the standard of

reasonableness [in applying the Delaney Clause] established by Congress." For good measure, the agency also cited *Monsanto Co. v. Kennedy* and several court decisions in non-FDA cases.

The FDA's decision on lead acetate was a new and important psychological step, explicitly shifting the official statutory focus from "Is it there?" to "Is it safe?" The issue arose from one of the statutory Delaney clauses itself, not from an exception clause (as in the no-residue problem), nor from the statutory definition of "food additive" (as in *Monsanto*). Moreover, the agency approved a carcinogen that was not an undesired residue or additive, but an active coloring ingredient deliberately administered to the human body. In such cir-

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cumstances, the FDA's decision to discount positive feeding studies was unprecedented. Apparently recognizing that fact, the agency attempted to minimize the importance of its decision, which, it said, was "based upon the unusual combination of scientific facts peculiar to lead acetate in hair dyes, a combination which will rarely, if ever, be presented again in this context." Once undertaken, however, fundamental policy change cannot so easily be arrested.

99 $\frac{44}{100}$ % Noncarcinogenic

The next problem to arise was that of carcinogenic constituents of food and color additives. No substance can be manufactured with absolute purity. How should the Delaney clause be interpreted when an additive is not itself carcinogenic, but contains an impurity known to be carcinogenic? Presumably, such an additive would have a carcinogenic effect attributable to the constituent impurity, whether or not conventional animal tests were sensitive enough to pick it up.

The FDA's approach during the 1960s and 1970s was generally to ban such additives. It made exceptions, however, for lead and arsenic, which are both animal carcinogens but are also

ubiquitous contaminants of additives (and foods generally) at extremely low levels. To have refused to make those exceptions would have been to ban all additives.

How should the Delaney clause be interpreted when an additive is not itself carcinogenic, but contains an impurity known to be carcinogenic?

Following *Monsanto* in 1979, the FDA began to develop a quite different approach to carcinogenic constituents of additives. It quickly came to the view internally that the Delaney clause applies only to whole additives, that issues concerning the risk from individual constituents can and should be handled under the general statutory requirement that additives be "safe," and that a carcinogenic constituent presenting a risk below a threshold would not trigger an automatic ban. Thus, if a whole additive was not found to induce cancer in a standard animal study, the Delaney clause would not apply against a trace carcinogenic constituent of the additive. This "constituents" theory complemented the agency's sensitivity-of-the-method technique, and the de minimis migration rationale developed in *Monsanto*. Any or all of the three could be used to address particular regulatory problems.

This new approach was eventually published in the *Federal Register* as an advance notice of proposed rulemaking in 1982. For the first time, the FDA announced a set of generally applicable rationales for approving directly ingested food and color additives that contain carcinogenic constituents. The agency stated three reasons for its change of policy toward constituents. First,

[o]ver the past twenty years, there have been rapid developments in analytical capabilities that make it possible to decrease by orders of magnitude the levels at which a component of a substance such as a food additive or color additive are detectable and identifiable. Many chemicals now can be identified and quantified at levels around one part per billion.

Second, more and more substances are being tested for carcinogenicity, and consequently

the list of animal carcinogens is growing. The likelihood that additives contain substances found to induce cancer in animals, therefore, grows as well. Third, the agency "is now confident that it possesses the capacity, through the use of extrapolation procedures, to assess adequately the upper level of risk presented by the use of a noncarcinogenic additive that contains a carcinogenic chemical." Assessing the actual risk is difficult and controversial because many quite different and plausible extrapolation models have been developed. Nevertheless, "there has been a growing recognition in the scientific community that by using certain conservative extrapolation models it is possible to estimate an upper limit of risk." In support of this proposition, the agency cited its 1979 sensitivity-of-the-method document and its 1980 decision on lead acetate.

On the day it published its new policy, the FDA approved D&C Green No. 6, a color additive for use in drugs and cosmetics that was not itself found to be carcinogenic, but contained a carcinogenic constituent. Approvals of other color additives and indirect food additives (including acrylonitrile) in similar circumstances followed. One such approval was upheld by the U.S. Court of Appeals for the Sixth Circuit in *Scott v. FDA* in 1984.

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Gradually, with each accumulating refinement of regulatory policy, the area of unqualified application of the Delaney clause was being eroded. The sensitivity-of-the-method approach had originally addressed carcinogenic substances that are administered to animals and do not leave detectable residues in human food. *Monsanto* addressed an indirect additive. Lead acetate was a topical cosmetic. D&C Green No. 6 was a direct food additive with a carcinogenic constituent. Could this developing approach, based on quantitative risk assessment, be applied to direct whole additives in human food that are themselves carcinogenic? Is there any remaining area where the Delaney clause

applies in absolute form? The next problem in the series squarely presented this final question.

The Final Step

In 1982 and 1983, the FDA concluded that six color additives themselves, not merely one or more of their constituents, had been shown to be animal carcinogens. Some of the additives had been provisionally listed for uses involving ingestion; others had been approved for external uses. The agency's National Center for Food Safety and Applied Nutrition and the commissioner of food and drugs recommended to the parent Department of Health and Human Services (HHS) that the six be banned. The Cosmetic, Toiletry, and Fragrance Association took the issue to the Office of Management and Budget (OMB) and also presented its views to the assistant secretary for health and to HHS Secretary Margaret Heckler.

The industry's position was, first, that five of the six additives present risks so low that they are de minimis and, therefore, under the evolving FDA policy, as stimulated and endorsed by the D.C. and Sixth Circuits, should be approved. Second, the industry argued, the remaining color additive induced a carcinogenic effect only by a secondary mechanism—that is, it did not cause cancer in animals directly, but only through an intermediate pathological state that would not occur in humans.

The FDA National Center's position was, first, that application of the de minimis principle to a direct whole food or ingested color additive would be contrary to the terms and intent of the Delaney clause; second, that in the case of the five color additives no risk assessment could in fact be done because color additives are complex mixtures, the specific carcinogenic agents in these additives have not been identified, the rates at which they are absorbed through skin are not established, and therefore exposure to the carcinogenic agent cannot be estimated; and third, that there is insufficient evidence that the sixth color additive produces cancer through a secondary mechanism.

In the June 26, 1985, issue of the *Federal Register*, the FDA announced that it was referring all the scientific issues—including the feasibility of quantitative risk assessments for these additives—to a panel of HHS scientists

outside the National Center. The clear, but unstated, implication of this action is that the agency is now prepared to apply the de minimis principle to direct food and color additives that cause cancer in animals.** Five days earlier, the agency denied a public interest group's petition to ban the additives. There, it expressly asserted that the de minimis doctrine applies to the Delaney clause.

The agency might have determined that the de minimis point is below the "safe" level of one in one million lifetime risk—say, at one in one hundred million over a lifetime. Between that level and the "safe" level, Delaney might apply. Such a scheme, which would have preserved some (albeit a reduced and arguably illogical) function for the Delaney clause but might not have preserved the colors, was considered but rejected.

There is overwhelming evidence, presented at a congressional hearing, that Secretary Heckler personally or someone on her immediate staff overruled the National Center (with or without pressure from OMB). Although Secretary Heckler's name generally appeared on major FDA decisions, it did not appear on this one—so that the decision was announced not with a bang but a whimper. The *Wall Street Journal*, however, did not miss its significance. In an editorial on the day the decision appeared in the *Federal Register*, the *Journal* commented that

the whole beleaguered Beltway culture could immeasurably improve its image with the rest of the country if every bureaucrat and congressional staffer in town carved these two useful words into his desk as the capital's new motto: De Minimis.

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How evaluate this consistent evolution of policy spanning twelve years and four administrations? Scientific facts and progress—in analytical chemistry and quantitative risk assessment—have clearly driven the process. Law

**In a proposed rule published in the *Federal Register* on December 18, 1985, the FDA proposed to ban the use of methylene chloride in cosmetics because it causes cancer in lab animals, but declined to lower the maximum residue of it permitted in decaffeinated coffee because that amount is considered safe.

has played a subordinate part: legal interpretation has adjusted to growing scientific knowledge and analytical sophistication. Moreover, with a solid push from the D.C. Circuit in *Monsanto*, the agency has used its creativity to infuse into the Food, Drug, and Cosmetic Act its growing confidence in quantitative risk assessment. Overt ideological preferences, other than to avoid taking regulatory actions that are manifestly foolish, came into play, arguably, only at the last stage.

Moreover, a powerful argument can be made, on grounds of policy, that if quantitative risk assessment is acceptable for carcinogenic animal drug residues, substances migrating from packaging materials, topically applied colors, and constituents of additives, then it should be equally acceptable for carcinogenic whole additives that are ingested. If we can say, with a high degree of confidence, that a risk really is de minimis, then a regulatory agency should be free to disregard it, whatever its source and nature. The series of regulatory developments just described illustrates the ra-

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tional elaboration of a major and sound approach to regulation. Once that process gathers momentum, obstacles in its path begin to crumble unless fortified artificially.

One may doubt, however, that the FDA's latest decision shows adequate respect for either the scientific prerequisites for risk assessment or the role of Congress in setting fundamental public policy. On the facts concerning these color additives, it is debatable whether they presented an appropriate occasion to decide that the Delaney clause is subject to quantitative risk assessment across the board. Moreover, there is a crucial question of legal process, of the appropriate roles of agency and legislature. For more than twenty-five years it has been the settled understanding of both
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the free world's oil came from OPEC states; now the proportion is about half that. The United States is buying vastly more from Mexico, Great Britain, and Canada. Nigeria's exports to the United States have fallen by four-fifths, and President Reagan, unlike his predecessor, need not hold African policy hostage to the whims of that or any other country.

The Lessons of Twenty Years

Not every federal regulation led to disaster. At a cost of roughly \$1,000 per new car, pollutants have been cut 80 percent since the 1960s. Traffic fatality rates are a mere half their 1966 peaks. But the overall energy fiasco of the 1970s was a different matter, mostly suggestive of economic irrationality and political opportunism.

In the years since, events have vindicated "conservatism," not as an ideology but as a collection of tenets for sensible living. Sooner or later, there will be links between cause and effect, pain and gain, power and responsibility. Presidents Eisenhower and Ford understood that; Presidents Nixon and Carter had other ideas. If only this brand of conservatism had been applied more deliberately, we might rest assured that Washington's regulators had learned something. We shall see. At any rate, we continue to reap rewards from the sacrifices of 1979-82.

One thing is certain. Since World War II, when gas is down and GNP is up, Americans prefer big, sporty, or powerful cars. No surprise therefore that, since the last recession, that is what we are back to. ■

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supporters and critics that the Delaney clause manifests an intent to accept no risk of human cancer from food additives, and that no threshold for carcinogens can be identified. That may no longer be good public policy, but there can be little doubt that that is how the Delaney clause has been widely understood.

So, although it is possible to agree that extending quantitative risk assessment to direct additives would be good public policy and a logical extension of prior regulatory decisions, it does not follow that such a decision should be left to the FDA. Such a dramatic departure from years of interpretation and public policy ought to be made by the Congress. By overturning a settled interpretation and policy in connection with these color additives, the agency places at risk its scientific credibility, its fidelity to law, and its political stature. This past June, before the agency's decision on the carcinogenic color additives, the House Committee on Government Operations issued a report that concluded without objection from any member—Democrat or Republican—that the FDA's failure up to that point to ban these additives was "in clear violation of the requirements of law." The agency's failure to ban the additives is also currently under challenge in U.S. District Court in Washington.

Some may believe that these risks to the agency are worth taking in order to torpedo the flagship of the health protection forces that prevailed during the roughly two decades prior to the 1980 elections. But on a neutral and longer view of the process of policy development, I would argue that the FDA has acted prematurely. For major regulatory change to be stable, it must be accepted, at least tacitly, by the Congress. Because the FDA's general policy has broad support outside as well as within the agency, the Congress may still ratify it through a change in law (twelve of the sixteen Republicans on the House Government Operations Committee have recommended this course). But because the agency acted unilaterally, and arguably beyond its authority, it has created a substantial risk of being overruled in court or of creating a congressional backlash. All of us who care about sound policy may be the losers. ■