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Regulation of carcinogenic food additives in the United States

La regolamentazione degli additivi alimentari cancerogeni negli Stati Uniti

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Summary

Regulation of food additives, including carcinogenic food additives, in the United States, is the responsibility of the U.S. Food and Drug Administration (FDA). FDA has approved for marketing food additives that have not been demonstrated, using good testing methods, to be free of carcinogenic potential. Acesulfame potassium, a high-intensity artificial sweetener, is widely used in the United States, usually in blends with aspartame or sucralose. Acesulfame has never been tested in bioassays sufficient to resolve the question of whether the additive is free of carcinogenic potential. FDA's decision-making regarding carcinogenic food additives has not necessarily been based on good science or protection of public health. Changes in the Food Additive Petition (FAP) approval process are needed to ensure that carcinogenic food additives do not get approved for marketing. Eur. J. Oncol., 14 (2), 79-92, 2009

Key words: **food additive, Food Additive Petition (FAP), acesulfame, carcinogens, U.S. Food and Drug Administration (FDA), carcinogen bioassay, U.S. National Toxicology Program (NTP), saccharin, aspartame, olestra**

Riassunto

La regolamentazione degli additivi alimentari, compresi gli additivi alimentari cancerogeni, negli Stati Uniti è di competenza della Food and Drug Administration (FDA). La FDA ha approvato la commercializzazione di additivi alimentari dei quali non è stato dimostrato, sulla base di adeguati metodi di analisi, che siano privi di potenziale cancerogeno. L'acesulfame potassico, un dolcificante artificiale di elevata intensità, è largamente usato negli Stati Uniti, solitamente in miscela con aspartame o sucralosio. L'acesulfame non è mai stato studiato con saggi adeguati per risolvere il quesito del suo potenziale cancerogeno. I criteri della FDA riguardanti gli additivi alimentari cancerogeni non si sono necessariamente basati sulla buona scienza o sulla protezione della salute pubblica. Sono quindi necessari cambiamenti nella procedura di approvazione di Richiesta di Additivi Alimentari (FAP) allo scopo di garantire che additivi alimentari cancerogeni non abbiano il benestare per la commercializzazione. Eur. J. Oncol., 14 (2), 79-92, 2009

Parole chiave: **additivo alimentare, Richiesta di Additivi Alimentari (FAP), acesulfame, cancerogeni, U.S. Agenzia per gli Alimenti e Farmaci (FDA), saggi di cancerogenicità, Programma Tossicologico Nazionale Americano (NTP), saccarina, aspartame, olestra**

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Documents used in preparation of this report

Certain documents used in preparation of this report were obtained during review of FDA public dockets in 1994-1996. U.S. Food and Drug Administration (FDA) internal memos were obtained during that review, in addition to public comments (including comments from companies and organizations supporting or opposing approval of a Food Additive Petition (FAP) for acesulfame) on FDA actions concerning that food additive. Letters from the Center for Science in the Public Interest (CSPI) to members of the staff of the U.S. National Toxicology Program (NTP) and letters from NTP and/or National Institute of Environmental Health Sciences (NIEHS) to CSPI or Myra Karstadt were also consulted.

Introduction

Increased use of processed foods in the United States has resulted in a major increase in exposure of Americans to food additives. Even raw food, such as chicken, may contain additives. Among the many additives currently being consumed by Americans are some chemicals known or suspected to cause cancer (saccharin, cyclamates, several food colors, acesulfame potassium, aspartame). There is at least one food additive (olestra) that, while it is itself not suspected of being a carcinogen, acts in such a way as to remove from the body nutrients that may prevent cancer.

Food additives comprise one of the groups of chemicals regulated by the U.S. Food and Drug Administration (FDA). The Center for Food Safety and Applied Nutrition (CFSAN) is the organization within FDA responsible for regulation of food additives.

FDA is currently paying little attention to food additive safety, and that situation is likely to get even worse over the next several years. At present, concerns about food safety are focused on bacterial contamination of produce (spinach, tomatoes, peppers, pistachio nuts) and processed foods such as peanut butter, another of the product groups regulated by CFSAN. It appears possible that within the next few years that regulatory responsibility will be removed from FDA to a new food safety agency. Food additives will be left behind at CFSAN, along with cosmetics, another little-regulated product category.

Even with food safety leaving FDA, it is unlikely that more attention will be paid to food additive safety. The recent passage by Congress of legislation giving FDA jurisdiction over tobacco products, most notably cigarettes, pretty much guarantees that several years and a great deal of attention by senior management at FDA will be spent on setting up and staffing the new tobacco regulatory structure within the agency. Those efforts could distract from attention that could have been paid to food additives and cosmetics.

One reason so little has been done – and is being done – to ensure that food additives that could cause cancer are not entering the food supply is public apathy. Historically, whatever pressure there has been on the agency in the field of food additive safety has come almost completely from companies wishing to get their additive products onto the market or keep those additives on the market in the face of evidence that the products may be unsafe. One national public health advocacy organization has challenged FDA decisions on food additives, but that organization's efforts are vastly exceeded by those of industry, industry consultants, and organizations which present industry views.

Food additives

Food additives are defined by the 1938 Federal Food, Drug and Cosmetic Act (FFDCA), as enacted in 1938 and amended subsequently (1).

A direct food additive is deliberately added to a food product to provide desired characteristics such as flavor, fragrance, "mouth feel", texture, thickness or stability in heat and/or cold. Color additives are frequently used in processed foods, and sometimes on raw products as well (as, on skins of certain citrus fruit).

Indirect additives enter foods by leaching out of machinery used in food processing, food containers (as, plastic bottles that contain cooking oil or other fatty foods) or food packaging (wraps, boxes).

Procedures for regulation of food additives in the United States

Food additives (including color additives) are essentially cosmetics for food. Cosmetics are products that can make people more attractive but, by definition in the FFDCA (2), do not affect the physiology or structure of the human body. When regulating drugs, which do affect the physiology or structure of the human body, FDA considers both the efficacy and safety of the medication. However, FDA and the legal system really don't care whether a lipstick color is particularly attractive or whether a flavoring makes a product taste very "chocolatey." The only attribute that matters for "people cosmetics" and "food cosmetics" (food additives) is safety.

Both food and color additives are subject to preclearance for safety under terms of the FFDCA. Under that law, marketers of food additives must submit a Food Additive Petition (FAP) for each product and intended application of a food additive. That is, if a marketer intends a fat substitute to be used in cookies and other baked goods, the FAP will specify that application. Of course, a marketer would hope to get the broadest possible approval for an additive, so for additives that can be used for a wide spectrum of applications, the ultimate goal is to get an approval for use in any foodstuff for which the additive is suitable.

Any food product that contains a food additive that has not been approved by FDA can be considered adulterated, and is subject to seizure by the U.S. Government.

The procedure for approval of an FAP includes submission by an additive's would-be marketer of safety data for the additive under review. FDA staff and management analyze the data submitted by the company, and prepare risk and exposure estimates. Calculation of a margin of safety (MOS) is important; that provides some idea of FDA's judgment of the ratio between the toxicity of a chemical and likely intake by a human. The type of toxic effect from which a MOS is calculated is important, since toxicity levels for carcinogens are typically lower than those for non-carcinogenic chemicals. However, within the past twenty years, industry-influenced arguments based on "mechanistic toxicology" have resulted in changes in presumptions as to the likely impact of chemicals that cause cancer in animals for people, and have also resulted in considering some carcinogens to be chemicals with thresholds, allowing, in both cases, for elevation of levels considered to be toxic. Elevation of estimated toxicity levels, if exposure levels remain constant, will inevitably result in elevation of the MOS, and reduction of apparent risk attributable to consumption of a given food additive.

Margins of safety can vary for different parts of a population, depending on food consumption patterns, so it is appropriate for FDA to do its calculations of margin of safety based on a high-consuming population. Children also require special consideration, since their small body size does not prevent them from consuming surprisingly large quantities of certain foods and beverages.

Working from a margin of safety, FDA staff can calculate an allowable daily intake (ADI) for a particular additive and a specified population. Again, conservatism should be expressed by setting the ADI low enough to take into account children, people with diseases and disabilities, pregnant women, and other populations that may be particularly vulnerable to adverse effects of the additive.

Since food additive petitions typically "start small", with approval for a limited use, if it is possible that use may extend beyond the application for which initial approval is sought, it becomes critical to ensure that exposure estimates and MOS and ADI calculations will be realistic if and when approved uses increase.

Activities at FDA concerning the Delaney Clause

Americans' concern about cancer was heightened in the period immediately following World War II. This heightened concern was likely due in good part to improvement in diagnosis of cancer, so that more cases were being identified, as well as advances in epidemiology, which was tracking cancer in the United States population.

Increased availability of data on cancer in humans and experimental animals coincided with major advances in analytical chemistry, such that limits of detection were being driven lower and lower.

Remarkable sensitivities were identified for analytical procedures for chemicals such as food additives.

In 1958, taking public concern about cancer into account, and acknowledging that chemicals such as food and color additives could be potential carcinogens (based in part on data becoming available from studies in experimental animals), Congressman Delaney of New York City introduced what has become known as the Delaney Clause (3). The Clause provides that any non-zero level of a chemical known to cause cancer in humans or animals in a food or color additive renders the product adulterated (4, 5). The combination of the Delaney Clause and increasing sophistication of analytical chemistry presented a dilemma for companies that marketed food and color additives. The Delaney Clause requirement that food and color products be free of carcinogenic chemicals – with analytical procedures able to detect lower and lower levels of carcinogens – represented a perceived barrier to industry growth. The companies concerned included those directly in the business of marketing additives. Manufacturers of processed foods, which became important in the United States during and after World War II, and which were heavily dependent on additives, would likely also have had concern about the possible impact of regulation on use of food additives.

FDA has attempted to deal with problems for industry caused by the Delaney Clause by using a variety of approaches to justify allowing carcinogenic food additives onto the market and keeping them there.

NCTR and Mega-Mouse

The National Center for Toxicological Research (NCTR), located in Pine Bluff, Arkansas, was set up to serve as FDA's toxicology laboratory. NCTR's mission should have been to provide FDA with high-quality science to support regulatory decision-making.

However, NCTR is likely best known for an experiment designed to establish a threshold for carcinogens, an early effort by FDA to avoid applying the Delaney Clause.

The Delaney Clause represents a "zero-exposure" approach to carcinogen regulation and, by implication, the science underlying that regulation. That is, no non-zero amount of a carcinogen can be considered safe. If there were a way to demonstrate that thresholds did exist, consistent with what had been established in classical toxicology for acute effects of many chemicals, Delaney would not be necessary and carcinogenic chemicals could be allowed on the market at detectable levels so long as the estimated threshold was not exceeded.

In order to explore the possibility of demonstrating a threshold for carcinogens, in the 1970s, NCTR carried out the "mega-mouse" experiment. The experiment utilized 24,000 specially bred mice, and 2-acetylaminofluorene (2-AAF) as the test agent. Despite the enormous investment of time and resources in the mega-mouse study, no threshold could be demonstrated (6).

The *de minimis* approach to avoiding application of the Delaney Clause

Color additives have been a particularly vexing product group for FDA, with some colors used not only in food, but also in drugs and cosmetics (some colors are used in drugs and/or cosmetics only, and not used at all in foods). Typically, cosmetic uses of color additives involve only external application (although toothpastes classified as cosmetics and mouthwashes similarly classified may be swallowed), but uses in food and drugs both can result in ingestion of color additives.

FDA attempted to avoid the strictures of Delaney by using risk analysis to demonstrate that non-zero quantities of color additives could present such a minimal risk of cancer that they could be used safely and therefore approved for sale, notwithstanding Delaney. That *de minimis* approach was overruled in an important court case (7).

The constituents approach to avoiding application of the Delaney Clause

FDA developed the "constituents" approach for avoiding application of the Delaney Clause, which approach appears to have prevailed, in court, for both food and color additives (8).

An explanation of the constituents approach has to take into account both contaminants of a pure additive and the presence of a pure additive in a chemical mix that may include carcinogens.

If an additive is manufactured using a process that generates one or more carcinogens, traces of which appear in the final color product, but the pure additive itself is not carcinogenic in humans or animals, FDA can approve listing the food or color additive.

If the marketed version of a food or color additive contains chemicals other than the additive – for whatever reason – and those additional chemicals are carcinogens, so long as the additive itself is not carcinogenic according to FDA's standards, the additive can be approved.

FDA actions in regard to individual food additives reveal flaws in the review and regulatory process

The author has been particularly interested in regulation of acesulfame, an artificial sweetener. This discussion will focus on that additive, but several other additives will be discussed as well.

Acesulfame

Acesulfame potassium (CAS RN 55589-62-3) (henceforth referred to as acesulfame) is a high-intensity artificial sweetener, 200 times as sweet as sugar (sucrose) (9). Acesulfame was developed by Hoechst, the German chemical company, which submitted the initial and certain subsequent FAP to FDA. As is the case for sucralose (Splenda®), another new-generation high-intensity sweetener, acesulfame can be baked or frozen without losing its sweetening capabilities. That is very different from sweeteners such as saccharin and aspartame, which cannot be subjected to extreme temperatures. Acesulfame can stabilize aspartame's sweetening ability, enabling aspartame to remain sweet long after aspartame alone would have lost sweetening power. Acesulfame is used in a very broad range of products, including cookies, ice cream, soda, dry drink mixes, and light orange juice.

Typically, acesulfame is used in blends, most notably with sucralose. Although Splenda's presence is usually advertised on the front of a package label, acesulfame's presence tends to be completely unheralded, appearing only in what is sometimes a very long list of ingredients on the back label.

Approval of the initial FAP for acesulfame rested on flawed toxicity data

The discrepancies between test protocols and implementation of Hoechst's 1970s tests of acesulfame and protocol and implementation requirements for National Toxicology Program (NTP) bioassays (10) are striking.

A. Randomization of animals to test groups was not carried out in the Hoechst tests

In order to ensure that results of a bioassay are relevant to other experimental animals and, ultimately, to humans, animals used in studies must be randomized to test groups. That is, animals of the same age should be distributed randomly (according to computer programs) into the various test groups. That is required for NTP bioassays. However, it was not done for either of the Hoechst rat studies. No information was identified on randomization in the test carried out in mice (11).

FDA's internal memos recording staff analysis during review of the initial acesulfame FAP include admissions by Hoechst and its contract laboratory of non-random selection for the acesulfame studies (12).

B. Subchronic studies were not carried out for each group of experimental animals

The only group of animals for which the Dutch laboratory that ran the acesulfame studies carried out a subchronic test was the rats used in the first of two rat studies, and, although the MTD estimated from that test was carried over to the second rat and mouse studies, the first rat study's results were discarded, and the strain of rats used in that study discarded as well (11).

C. It is likely that MTD was not attained in the animal tests, reducing their ability to predict potential carcinogenicity

As noted above, there was only one subchronic test for the three animal test groups in the Hoechst acesulfame studies. MTD for subsequent studies – and for the NTP tests in GMM mice – was set based on that one test, and, as noted by NTP (13), may have been too low. Setting the MTD too low would reduce the ability of a test to detect carcinogenicity in test animals.

D. The Hoechst mouse study was too brief in duration

Standard NTP bioassays hold animals on treatment for 104 weeks (two years) after weaning, with all animals sacrificed at the end of that time.

The Hoechst mouse study was only 80 weeks in duration (14), but FDA accepted results of that study.

E. Animal husbandry and collection of tissues for microscopic pathology were inadequate

Accounts of poor animal husbandry at the TNO laboratories where Hoechst's acesulfame tests were carried out can be found in FDA internal memos from the period when the agency was reviewing the initial acesulfame FAP.

One important aspect of the TNO studies was the laboratory's failure to collect sufficient numbers and types of tissues for microscopic pathology examination (15). The NTP bioassay program requires full examination of tissues from a long list of organs for all animals in the study groups - controls, high-level, mid-level (10). The Hoechst studies, on the other hand, either failed to take tissues from, in particular, mid-level animals, or took so few tissue samples as to make it impossible to achieve statistical reliability.

When it became clear that the Hoechst tissue collection methods didn't comport with the standards in the FDA "Red Book" (16) then in use, the agency could have required Hoechst to repeat their animal tests. However, rather than do that, FDA allowed Hoechst to hire a consultant pathologist to rummage through tissue pots for animals from which insufficient tissues were taken, collect what had been missing tissues, and carry out pathology on those tissues (17). Allowing Hoechst to re-do tissue collection reduces confidence in the tests as a whole.

F. FDA excused Hoechst's non-compliance with guidelines for testing set out in the agency's own "Red Book"

FDA has criteria for conduct of toxicology tests; those criteria are set out in the FDA "Red Book" (16). Requirements set out in the Red Book applicable at the time (1980s) the acesulfame tests were under review cover such topics as randomization of animals to test groups, establishment of an MTD through subchronic testing, and holding animals on test for a time sufficient to provide a good chance of eliciting carcinogenic responses. The acesulfame tests failed to meet several of the criteria. When challenged as to the failure of the acesulfame tests to meet Red Book standards, FDA has stated that the Red Book sets out guidelines only, and there are no set requirements for conduct of tests to be used to support FAPs. When it has been pointed out that the acesulfame tests in no way resemble the standards set out in NTP's bioassay guidelines, FDA has replied that the NTP standards have no regulatory status, and are irrelevant to FDA's approval process (8).

G. FDA's approval of acesulfame based on Hoechst's inadequate animal tests contradicts basic conservative practice of public health

An important consideration in practice of public health is the extent to which people are going to be exposed to an agent or a category of agents. Where large numbers of people are going to be exposed to potentially high levels of an agent or category of agents, there should be a high level of assurance that the agent is safe. That is, as potential exposure increases, certainty that an agent is safe should also increase. Certainty can only be assured when tests on which decisions about which an agent are based are excellent; test protocols and implementation of those protocols must be of the highest quality. That was certainly not the case with acesulfame which, although hardly in use at all when the first FAP approval was granted in 1988, could reasonably have

been expected to reach very high levels of exposure if and when approval was granted for use in soda and/or general use. Of course, what made high-level exposure to acesulfame happen was use of the sweetener in blends with sucralose, currently the most popular artificial sweetener in the United States.

The popularity of sucralose was not anticipated in the 1980s, but the possibility that acesulfame would attain high exposure at some time was anticipated by members of FDA's toxicology review staff. Those staff members, most notably Dr. Linda Taylor, called attention to the flaws in the Hoechst tests and warned that the studies, even if minimally acceptable in 1980, might very well not suffice if and when acesulfame came into greater use. In 1986, Dr. Taylor noted that: "*The question remains whether these studies are sufficiently definitive or rigorous in light of the potential for widespread, high exposure to acesulfame potassium in all group [sic-MLK] in the population*" (14). In a memorandum of a 1986 meeting between FDA review staff and representatives of Hoechst, FDA reviewers noted that they had told Hoechst that: "*We consider that any further consideration of other uses of this sweetener may show the need for additional supporting data*" (18).

Problems with FDA's regulation of acesulfame continued after the first FAP for the additive was approved

Procedural problems at FDA placed roadblocks in the path of effective regulation of acesulfame after the initial FAP for the additive was approved in 1988.

Once FDA had approved acesulfame, challenges to the data supporting approval were routinely rejected

The Center for Science in the Public Interest (CSPI), a public health advocacy group specializing in food-related issues, filed its first objection to approval of the FAP for acesulfame in 1988, shortly after the sweetener was first approved for use. The challenge, which reviewed certain inadequacies in test design and implementation, was rejected by FDA. The reason the agency gave for the rejection was the same as that given for all subsequent challenges: CSPI had not submitted any new data to refute the results of the Hoechst studies (8).

It appears that the only way a challenge could have been made to approval of acesulfame would have been for CSPI to conduct its own animal tests and submit results from those new tests to FDA. It is unreasonable to expect public interest groups to carry out or sponsor animal bioassays; those groups do not have the resources of industry or the federal government.

Protocols for the Hoechst studies are seriously out of date

The Hoechst animal studies were carried out in the Netherlands in the mid-1970s. FDA began their review of the acesulfame toxicity data in 1980. Initial approval of acesulfame for use in foods was granted in 1988, and FDA appears to have considered the science to have been settled at that time.

Test protocols for studies in animals of carcinogenic potential were under development in the 1970s. In 1996, at the request of CSPI, Dr. Umberto Saffiotti, who headed the organization at the National Cancer Institute (NCI) that focused on development of test protocols for chemical carcinogens, reviewed the Hoechst test data. Dr. Saffiotti noted the inadequacies of the protocols, in light of developments in testing protocols during and since the 1970s. He noted that results of the acesulfame subchronic test were reported in 1974, the results of the first rat study in 1976, and the results of the mouse study in 1979; those reporting dates would place protocol design for the tests in the early 1970s. In the early 1970s, according to Dr. Saffiotti: "…*the standard criteria for the design of animal carcinogenesis bioassays were still under development*" (19). NCI's "Guidelines for carcinogen bioassays in small rodents", the predecessors to the requirements used in designing and carrying out NTP bioassays, were published in 1976. Dr. Saffiotti then noted that:

"…*Reading the reports of the tests on acesulfame brought back to me the "flavor" of the bad testing practices that were common [in the early and mid-1970s-MLK], such as the use of poorly defined*

animal colonies, diffuse respiratory infections, lack of randomization in the assignment of the animals, limited sampling for histopathology, uncertainties as to what was the appropriate dose range to be tested…" (19).

The Hoechst test protocols were essentially out of date (as well as inherently flawed) when FDA began their review of the FAP in 1980. The test protocols were even more out of date in 1996, when FDA was considering the FAP for use of acesulfame in soda and when NTP received and rejected CSPI's nomination of acesulfame for testing in the NTP bioassay program.

FDA failed to require better tests of acesulfame when use of acesulfame in soda was under consideration

Use of artificial sweeteners in soda has traditionally been the major application of those food additives. In the mid- and late-1990s, when FDA was considering the FAP for use of acesulfame in soda, the agency could have required Hoechst and/or Nutrinova, the U.S. marketer of acesulfame, to conduct well-designed and properly implemented tests of the sweetener. FDA did not do so.

FDA prevented NTP from carrying out bioassays of acesulfame

The United States National Toxicology Program (NTP) is a multi-agency organization, situated in the Department of Health and Human Services (DHHS). NTP is physically situated in Research Triangle Park, North Carolina, and is administered as part of the National Institute of Environmental Health Sciences (NIEHS), which is one of the National Institutes of Health (NIH). NTP, established in 1976, has as its mission design of protocols for studies of toxic effects of environmental chemicals and implementation of those protocols in studies conduced by or for NTP.

Federal government agencies within and outside DHHS are members of NTP; FDA is a member agency.

In 1996, CSPI, aware that FDA was considering approving acesulfame for use in soda, and very well aware of FDA's reluctance to remove the sweetener from the market or order new tests, nominated acesulfame for testing in the standard NTP two-year bioassays (20). Those bioassays have long been considered the "gold standard" for long-term toxicity tests in the United States.

The nomination documents (20) make it clear that the Hoechst tests of acesulfame in no way resemble those conducted under NTP bioassay criteria. Although at that time acesulfame was very little used, it was apparent that if FDA were to approve the FAP for use of acesulfame in soda, the sweetener would be consumed by large numbers of Americans. NTP starts few bioassays each year, and the number of bioassays started each year has dropped within the past decade, but nomination of a chemical with potential for widespread exposure and very poor tests done previously should have merited serious consideration for inclusion in the bioassay program.

The nomination of acesulfame for testing by NTP was rejected.

Documents obtained recently indicate that FDA did not want acesulfame tested, and made its wishes known to NTP staff (21). It appears that the agency under whose jurisdiction a chemical falls has what amounts to a veto over testing by NTP, and FDA appears to have exercised their veto in 1996.

Acesulfame came into wide use in the early 2000s, in large part because of the great popularity of sucralose (Splenda), an artificial sweetener with which acesulfame was often blended (use of acesulfame alone is very rare). Sucralose having replaced aspartame as the most popular artificial sweetener in the United States, acesulfame usage also rose significantly.

Noticing the great range of products containing acesulfame available in grocery stores, in 2006 the author submitted a second nomination of acesulfame for testing in the NTP bioassay program (22). Once again, the nomination was rejected.

Uninformative tests of acesulfame using genetically modified mice (GMM) took place under the auspices of NTP

Documents obtained recently indicate that in the late 1990s, at a time when FDA objected to having

acesulfame tested in NTP bioassays, FDA, in agreement with NTP management, supported testing of acesulfame included in genetically modified mice (GMM) (23). Several GMM strains were then being validated by NTP, to see whether results obtained with the engineered strains would be consistent with and predictive of results indicating carcinogenicity in long-term bioassays.

The two mouse strains selected for testing of acesulfame (and aspartame) were unlikely to provide meaningful data on potential carcinogenicity of either chemical, since neither chemical is genotoxic, and one of the two tests was not a carcinogenicity test. The test that does assay for carcinogenic potential appears to be considerably more sensitive to genotoxic chemicals than to non-genotoxic chemicals.

NTP scientists identified acesulfame as a "negative control" in the GMM studies (13), fully expecting that the chemical would test negative. Indeed, that was what happened.

That the NTP GMM test did not yield positive findings acesulfame has been cited by industry (24) as proof that acesulfame does not cause cancer and is safe for use as a food additive.

Results of the GMM studies should have resulted in full two-year bioassays for acesulfame

If public health considerations had been taken into account, the GMM tests would have simply been deemed uninformative and acesulfame moved into the queue for testing in an NTP bioassay. In 2003, at the time of the initial release of the results of the GMM studies, Dr. Martha Sandy of the California Office of Environmental Health Hazard Assessment (OEHHA) discussed the importance of conducting bioassays when unvalidated GMM studies yield negative results (25). She stated that, given that the "*apparent inconsistency and insensitivity between transgenic and rodent lifetime bioassay results presently cannot be explained…negative results cannot be interpreted clearly. Thus, compounds giving negative results in transgenic assays must be further tested in two-year bioassays*".

She stated further that "...*Given recognized limitations of the [two GMM test systems used to assay acesulfame and aspartame-MLK] transgenic models… negative results are not informative as to the test substance's carcinogenicity, and point to the need to conduct standard two-year carcinogenicity studies… At this time, [2003-MLK] transgenic models cannot replace the two-year bioassays and it would be unwise to list a chemical as safe for human exposure or consumption based upon negative results in not-yet-validated model systems*" (25). As of 2009, those models continue to be less reliable than two-year bioassays for establishment of carcinogenic potential.

Unfortunately, as noted above, representatives of the food industry have used the NTP GMM results to support their contention that acesulfame does not cause cancer and therefore does not need testing in a bioassay.

A 2008 letter from Dr. Samuel Wilson, Acting Director of NIEHS/NTP, to Chris Van Hollen, a United States Congressman, describes the reasoning NTP and FDA used to deny testing in a bioassay for acesulfame after the sweetener tested negative in the GMM systems (23). Based on Hoechst's animal tests and the results of the GMM studies, Dr. Samuel Wilson, then Acting Director of NIEHS, stated to Congressman Van Hollen that there was no need for bioassays:

"…*In response to [CSPI's 1996 nomination of acesulfame for testing in the NTP bioassay program-MLK], the NTP carried out toxicology studies in genetically modified mice… Following the publication of these studies, the CSPI*[1] *again nominated acesulfame potassium for carcinogenicity testing in 2006. Based upon the findings from the aforementioned studies, and in consultation with the FDA, a member agency of the NTP, it was determined that additional testing of acesulfame potassium was not warranted at this time*".

It is interesting that acesulfame was tested in the two GMM systems along with aspartame, a food additive for which recent bioassays carried out in Italy established that aspartame is a multi-site carcinogen (26). Aspartame also tested negative in the two GMM systems (13).

[1] The 1996 nomination of acesulfame for testing in the NTP bioassay program was submitted by Myra Karstadt and Michael F. Jacobson on behalf of the Center for Science in the Public Interest (CSPI). Myra Karstadt filed the 2006 nomination as a private citizen unaffiliated with CSPI.

FDA used the constituents policy and *de minimis* to excuse contamination of acesulfame with known carcinogens

The Federal Register (FR) notice of approval by FDA of use of acesulfame in soda (8) includes a description of two potentially carcinogenic contaminants in the food additive. FDA used two approaches to avoid application of the Delaney Clause in order to approve use of acesulfame in soda.

A breakdown product of acesulfame is carcinogenic in animals. In the FR notice, FDA stated that there was likely to be so little of that product that it need not be considered.

In addition, dichloromethane (methylene chloride), an animal carcinogen, is used in processing acesulfame. Since detectible levels of dichloromethane are present in acesulfame as it is formulated for sale, the Delaney Clause should have prevented approval of the additive for use in soda. However, FDA applied its "constituents" policy to justify approval of acesulfame, stating that since acesulfame itself was not a carcinogen, the presence of carcinogenic dichloromethane was irrelevant when approval of acesulfame for use was under consideration.

Potential carcinogenicity of acesulfame is a special problem because the public is receiving no warnings about the presence of the additive in foods

FDA requires label warnings for food additives demonstrated to cause health problems in people or which may be potentially hazardous to people. Thus, because phenylketonurics may experience adverse effects from consumption of foods containing aspartame, food products containing aspartame carry a warning label to that effect. Similarly, the sugar alcohols (xylitol, mannitol, etc.) can be used as sweeteners by those who cannot tolerate sucrose, but consumption of large amounts of sugar alcohols can result in digestive problems (laxative effects). Foods containing sugar alcohols bear a warning indicating possible laxative effects.

Since FDA concluded that acesulfame does not cause cancer in animals, or significant health effects in humans, there is no label warning indicating the presence of the artificial sweetener in processed foods. It is likely that very few people know that acesulfame is present in foods they are consuming, and it is likely that even fewer consumers are aware that acesulfame has never been tested sufficiently to conclude that the chemical is not potentially carcinogenic.

Would consumers buy fewer foods containing acesulfame if people were told the additive has not been shown to be safe? History suggests that people would go on eating (and drinking) acesulfame-containing products. Public pressure led Congress to enact laws that kept saccharin on the market after FDA banned the sweetener because it caused cancer in animals. Given the history with saccharin, certain coal tar hair dyes, and mega-vitamins/health foods, it's likely that, even with insufficient demonstration of non-carcinogenicity for acesulfame, the American public would insist that the sweetener be kept on the market.

There was pressure from economic interests to approve acesulfame

During the period when FDA was considering the FAP for use of acesulfame in soda (non-alcoholic beverages), the author reviewed documents in the FDA public docket established to hold documents pertaining to that FAP. The agency had received letters from Nutrinova, the would-be marketer of acesulfame (27), and a trade association representing marketers of artificially sweetened beverages (28), requesting expedited consideration of the FAP and emphasizing the importance of getting acesulfame approved for use in soda.

Regulation of other potentially carcinogenic food additives by FDA has also been flawed

Saccharin

The experience with saccharin is an example of regulation of a carcinogenic food additive being heavily influenced by parties outside the agency, without regard to safety.

Saccharin was the first artificial sweetener to become popular in the United States. Results of tests carried out in the 1970s indicated that saccharin (sodium saccharin) caused bladder cancer in male rats (29). Accordingly, FDA banned saccharin in 1977, acceding to the requirements of the Delaney Clause (30). Mechanistic toxicology has suggested that the saccharin-induced bladder cancers are specific to aging male rats, and, since humans are alleged to lack a biochemical pathway similar to that which causes the cancers in the male rat, the bladder cancers in male rats are alleged to be irrelevant to people (29). There is disagreement as to whether the mechanistic pathway is correct, and, even if it is correct, whether that pathway found only in rats is the sole pathway by which saccharin could cause human bladder cancer. Based on mechanistic considerations, the International Agency for Research on Cancer (IARC) has classified sodium saccharin as having "sufficient" evidence of carcinogenicity in experimental animals, but sodium saccharin, saccharin and all saccharin salts are considered to have "inadequate" evidence of carcinogenicity in humans (29).

Public reaction to the FDA ban on saccharin was swift and highly negative. Congress, reacting to the vociferous public opposition to FDA's ban on saccharin, enacted a law that permitted saccharin to be marketed despite its carcinogenicity. That law has been continued in force (30).

Saccharin is still in use in the United States. Some people still use saccharin as a table-top sweetener, preferring it to newer additives.

Citing conclusions from mechanistic toxicology, in 2000 the U.S. National Toxicology Program (NTP), after divided committee votes, removed saccharin from its list of potential carcinogens in people (31). The removal of saccharin from NTP's list of chemicals "reasonably anticipated to be a human carcinogen", also resulted in saccharin being removed from California's Proposition 65 list of chemicals "known to the state to cause cancer" (32).

Aspartame

FDA's treatment of aspartame provides a good example of the agency's failure to take into account newly developed data that indicate that an additive causes cancer. Approval for use of aspartame in foods was first granted in 1974 (33). Initial approval included a requirement that foods containing aspartame include a warning that the additive could not harm phenylketonurics, individuals with a hereditary gene-linked abnormality that prevents breakdown of aspartame and similar compounds.

Laboratory data identifying aspartame as a multisite carcinogen in experimental animals (rats) appeared in 2006 (26). The data were immediately attacked by industry and by organizations of food safety experts that have traditionally played a major role in serving as science advisors to WHO and other government entities (34).

As of early 2009, FDA does not seem to have taken steps to revise its earlier assessment of aspartame's carcinogenicity taking the new data into account.

Olestra

Olestra is an artificial fat that cannot be absorbed or metabolized by humans. Its marketing depends on Americans' antipathy to paying the caloric price for real fat but still wanting to eat the crispy and rich foods that depend on fat for their appeal.

Olestra (Olean®), a sucrose polyester, was the subject of a food additive petition submitted to FDA in 1990 by the Procter & Gamble Company (P&G) (35). P&G submitted a FAP to use olestra in "savory snacks," such as potato and tortilla chips, and savory crackers such as Ritz®.

Olestra, due to its being unabsorbed in the gut, slides through the intestine adsorbing fat-soluble nutrients encountered along the way. Thus, vitamins A, D, E and K as well as carotenoids would be adsorbed by olestra and retained by the artificial fat as it progresses through the gut. Since olestra is not metabolized, the chemical is not incorporated into stool, and can leave the gut in an oily discharge; the yellow-orange coloration of the greasy discharge is due to carotenoids (36).

Olestra itself has not been shown to be carcinogenic. However, it can remove lycopene, a carotenoid, from the body. A deficiency of lycopene, a carotenoid found in tomatoes, has been associated with an increase in the development of prostate cancer (37). Because of the possibility that olestra would strip lycopene and other important nutrients

from the body, nutritional epidemiologists throughout the United States, met at the Harvard School of Public Health and sent letters to FDA attempting to prevent approval of olestra (38). FDA did approve olestra, but required supplementation with vitamins A, D, E and K (39). However, despite widespread concern about the possible rôle of lycopene in prevention of prostate cancer, FDA declined to take into account the implication of depletion of carotenoids including lycopene.

A pharmaceutical capable of sequestering important fat-soluble nutrients, much like olestra, was approved for over-the-counter use in 2007 (40). Orlistat, marketed over the counter (OTC) as Alli, prevents breakdown of fats because it inhibits pancreatic lipase (40). Like olestra, Alli moves through the gut picking up fat-soluble nutrients, and like olestra, it can produce greasy stools and similar discharges. Orlistat is unlike olestra in that orlistat was shown to produce aberrant crypt foci in animal studies; those lesions are pre-cancerous intestinal growths (41). Despite those lesions and the likelihood that, like olestra, orlistat would strip potentially cancer-preventing lycopene, as well as other carotenoids, from the body, FDA approved the drug for over-the-counter sale. The approval for OTC sale included the recommendation that people using Alli take Vitamin A, D, E and K and beta-carotene (40).

Testing of food additives for possible carcinogenicity

Pre-market safety clearance of potentially toxic chemicals makes good sense. Testing is done before there is significant public exposure, and before economic forces are mobilized to protect an additive established on the market.

Food additives, like pesticides, industrial chemicals, and drugs (pharmaceuticals) are among the product categories that are subjected to pre-market safety clearance by a United States Government agency.

Safety clearance for cancer, through use of animal tests, has two critical parts: determining what constitutes "cancer", and devising test protocols/data analytical techniques that provide assurance that whatever effect is seen in a test is reliable.

Determining what constitutes "cancer" is not a self-evident matter. Over the past two decades, "mechanistic toxicology" has created a thought pattern inimical to public health principles. Using mechanistic toxicology, it may be possible to posit a mechanism idiosyncratic to a test animal and unlikely to occur in people. If cancer occurs in a test animal and a mechanistic explanation can be adduced to downplay the relevance to humans, should that animal cancer be considered "cancer" for purposes of regulation?

In addition to using an assortment of techniques to avoid application of the Delaney Clause, FDA has proven itself receptive to mechanistic explanations to avoid designating chemicals as carcinogens.

Safety pre-clearance is not so much a demonstration of safety, but a demonstration that a chemical is not unsafe according to a specified criterion. When it comes to cancer, a determination that a chemical is not carcinogenic depends on the credibility of the animal tests that have been carried out or, when epidemiology data are available, the credibility of those data.

In the case of acesulfame, the animal tests that were carried out on the chemical were highly inadequate, in no way consistent with criteria for good test design and implementation. Therefore, we cannot say with any confidence that we know whether acesulfame causes cancer in animals. FDA's decision to accept results from those flawed tests does not make them any more conclusive of evidence of carcinogenicity.

Industry-dominated "expert" organizations

When new data on carcinogenicity of aspartame in experimental animals were released, those data were immediately attacked not only by marketers of aspartame in the United States and abroad, but also by organizations that represent "experts" in the food additive field (34). Organizations such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA) have historically been constituted of consultants, some of whom are university professors, employees of the food industry and other scientists who represent food industry positions to various publics, including scientists and regulators the world over.

How can efforts to prevent carcinogenic food additives from getting on the market (and staying on the market) be improved?

It will not be easy to improve pre-clearance of food additives for carcinogenicity. It will not be easy to improve the likelihood that a carcinogenic food additive will be denied approval for marketing. There are several reasons why pessimism is justified.

First of all, the FAP review process is in good part closed to public scrutiny, unless public hearings are held to review an FAP. The Toxic Substances Control Act (TSCA) specifically provides that health and safety data are not eligible for designation as "confidential business information (CBI)", and other laws have similar provisions. It should be a priority to make all health and safety data submitted with an FAP public during the period when an FAP is under review.

A procedure currently in use for pesticide registrations could improve regulation of food additives: require re-approval of a FAP at specified intervals. Periodic re-approval would require updates of the toxicology literature, ensuring that recent findings like those indicating aspartame's carcinogenic potential could not be ignored. In addition, periodic re-approval should result in examination of the quality of test protocols used to obtain an FAP. If advances in methodology were taken into account in a re-approval process, the would deal with some of the problems encountered in regulation of acesulfame.

Due to the imbalance between industry and public interest groups when it comes to resources (including staff) needed for effective scrutiny of FAPs, even if health and safety data were readily available, it could be difficult to find experts to do paper reviews on behalf of the public.

Finally, only one public interest organization – the Center for Science in the Public Interest – has played a significant rôle in regulation of food additives, and that organization has many other important areas of interest, including food safety, and a limited staff and budget. More attention is needed from members of the public and the public interest community if FDA is to improve its current inadequate regulatory structure and activities in the area of regulation of food additives.

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