Sweet and Sour

The Unanswered Questions about Aspartame

by

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Several of the tests carried out to assess possible adverse health effects of the artificial sweetener, Aspartame, were investigated by the US Food and Drug Administration in the 1970s because questions had been raised about the conduct and reporting of the tests. In particular, there were doubts as to whether the tests could provide an adequate basis on which to assess the chemical's safety. As three pivotal tests have never been repeated, the public cannot be confident that Aspartame is safe. The way in which the decision was reached to allow this food additive onto the market has worrying implications for both public safety and confidence.

Most public disputes concerning the health effects of a product on sale involve differences of opinion about the interpretation of available scientific evidence. But the controversy over Aspartame, an artificial sweetener used in a wide variety of products, such as soft drinks, and marketed in Britain and other countries by NutraSweet under its own trade name,[1] concerns the authenticity and reliability of the evidence itself. The public has a right to assume that scientific tests on products are objective and thorough and have been carried out to the highest scientific standards. There is considerable evidence that, in the case of Aspartame, the tests were inadequate in all these respects.

Worrying Anomalies

Aspartame is a compound formed by combining two amino acids, namely aspartic acid and phenylalanine. In the early 1970s, a US pharmaceutical company, G.D. Searle, which owned the patent on the chemical, decided to market it as an artificial sweetener. In July 1974, the Food Bureau of the US Food and Drugs Administration (FDA) announced that it was satisfied that Aspartame was safe, and that it would shortly be allowed onto the US market. Subsequent work in the FDA's Drugs Division, carried out by Dr Adrian Gross, cast doubts about the safety of the chemical, however, and in December 1974, the FDA announced an abrupt change in its decision: the imminent introduction of Aspartame was to be postponed, pending the results of an urgent investigation.

The FDA decided to investigate Aspartame after Gross noticed what he thought was a worrying anomaly in a Searle report on another product, Flagyl: the summary at the start of a document did not accurately reflect the detailed data presented in subsequent chapters. The report was returned to Searle in the expectation that it would change the summary to fit the data. Gross was surprised when a fresh submission arrived with some of the data altered to fit the summary.[2] Officials from the Drugs Division then made an unannounced visit to the Searle's offices and laboratories, in the course of which questions were raised about the conduct and reporting of tests on the safety of Aspartame: as with Flagyl, the documents submitted by Searle did not accurately represent the conduct of the experiments which it was supposed to be reporting, and consequently may have underestimated the possible toxicity of the sweetener.[3] The FDA responded by establishing two task forces, one to concentrate on the pharmaceutical products and the other, within the Bureau of Foods, to concentrate on Aspartame.

The Bureau of Foods Task Force identified 15 studies on the safety and toxicity of Aspartame which it thought needed to be examined in detail so as to determine whether or not they had been properly conducted and reported. The FDA, however, claimed that it only had sufficient resources for its scientists to review just three of the 15 studies; it assigned the other 12 studies to be reviewed by an independent organization called Universities Associated for Research and Evaluation in Pathology Inc (UAREP), under contract to G.D. Searle. This announcement was puzzling. The FDA had just received fresh funding, following Senate Committee hearings, to enable them to scrutinize toxicological data from the chemical industry. Furthermore, Dr Gross had explained to his superiors that it was not only unsatisfactory for Searle to be involved in setting the terms of reference for the UAREP investigation, but also that UAREP did not possess the requisite expertise to rule upon the conduct of animal experiments. Gross considered that the main problem lay in the manner in which the studies had been conducted, yet UAREP was a professional organization of pathologists whose expertise lay in the interpretation of tissue samples, not in the conduct of experiments with live animals.

The Task Force Report

The research by the Bureau of Foods Task Force focused on three pivotal studies, two involving the possible effects of Aspartame on reproduction in rats and mice (including possible embryotoxicity), and one examining the possible carcinogenicity in rats of a decomposition product of Aspartame called diketopiperazine (DKP).[4]

The Task Force found "significant deviations from acceptable procedures for conducting non-clinical laboratory stud-

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ies"[5] in all three studies, its detailed investigations (known collectively as the Bressler Report) noting that Searle's conclusions failed to reflect accurately the raw data generated in the laboratories. In some cases, there were simply no data to back up the supposed results; in others, it was impossible to determine what were the original results and what were subsequent revisions or summaries. It was even impossible to identify from the laboratory records exactly when a particular animal had died. As the Bressler Report states: "Observation records indicated that animal A23LM was alive at week 88, dead from week 92 through week 104, alive at week 108, and dead at week 112".[6]

No fewer than 52 major discrepancies were found in the Searle submission on the DKP test alone.[7] The Task Force was unable, for example, to establish how much DKP had actually been consumed by the rats. The FDA investigators found no fewer than three separate documents with different specifications for the content and the purity of the test substance, and they were unable to establish precisely which specification, if any, correctly represented the material(s) used. It was impossible, furthermore, to reconcile the quantity of the chemical requisitioned from stores with the quantities supposedly fed to the animals. There was evidence indicating that the test substance had not been properly ground up, and had been inadequately mixed, so that the animals may have avoided the DKP while eating their food.[8]

A Startling Opinion

However, whilst admitting these discrepancies, the Task Force concluded that they "were not of such a magnitude that they would significantly alter the conclusions of the studies"[9] — a finding that startled many observers. Indeed, critics argued that, in reaching such a conclusion, the Task Force appeared to be repeating the same mistake for which it had criticized Searle, namely, that its summary failed to reflect accurately the information contained in the reports upon which it was supposed to have been based.[10] However, as Dr Jacqueline Verrett, one of the members of the Task Force, subsequently stated:

> "We were limited in what we could actually conclude about the studies. We were not allowed to comment on the validity of any study. It was an explicit instruction based on administrative rather than scientific considerations. We were supposed to figure out what the conclusions would have been if the studies had been fully and correctly reported. We were obliged to ignore the protocols and the non-homogeneity of the DKP. The Bressler Report did show that non-homogeneity. Some animals did reject the DKP. Searle initially said that it may not have been fully mixed but that it did not matter: they later said that it had been fully mixed. We were not allowed to consider those issues by the Bureau of Foods administrator . . . We were ham-strung in being able to comment. The fact is that the studies should not have been considered at all, and that was the position from the beginning."[11]

In 1978, UAREP delivered its 1062-page report, which concluded that the 12 studies it had audited were "authentic".[12] Until his death in 1992, Dr Gross continued to maintain that UAREP had replicated the shortcomings of the FDA Task Force report: it concentrated on the interpretation of samples of tissue on microscope slides rather than considering the procedures which had led to those particular tissues being placed on those slides.

Public Inquiry or Private Decision?

Despite the fact that these two reviews concluded that Aspartame had been properly tested and that the substance was safe, a vocal lobby in the US — including the Community Nutrition Institute led by James Turner and supported by Dr John Olney — was still not satisfied.[13] In 1979, in an attempt to resolve the controversy once and for all, the FDA set up a Public Board of Inquiry (PBOI) which presented its conclusions in October 1980.[14]

The PBOI confined itself to examining two questions, both relating to Aspartame's possible effects on the brain. It took the view, firstly, that Aspartame consumption would not pose an increased risk of brain damage resulting in mental retardation, but it concluded (by reference to data from two of the studies examined by UAREP) that it was unable to rule out the possibility that Aspartame could induce brain tumours. Consequently the Board recommended that Aspartame should not be permitted for use, pending the results of further tests.[15]

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However, the Board's role was merely advisory, and it was the responsibility of the FDA's Commissioner, Arthur Hayes Jr., to make a ruling. In July 1981, he announced his decision to approve the use of Aspartame in food products other than soft drinks.[16] He made it clear that he disagreed with the PBOI and that the available data were sufficient to persuade him that Aspartame did not cause brain tumours in laboratory animals.

Hayes was not a toxicologist, and his approval for Aspartame was opposed by several senior FDA scientists.[17] Subsequently, however, two of the three members of the Board revised their own judgement and decided that they agreed with Hayes.[18] For his part, Hayes left the FDA and, two months later, became a Senior Scientific Consultant to the public relations firm Burson-Marsteller, which has acted as a consultant to G. D. Searle and NutraSweet.[19]

In 1985, Searle was acquired by the major US chemical company Monsanto, which separated the Aspartame operation from the rest of its activities and placed it under the NutraSweet Corporation. NutraSweet has repeatedly claimed that all the safety tests on Aspartame were properly conducted, pointing out that no charges have ever been preferred.[20]

The absence of charges, however, would appear to have been in spite of, rather than because of, the efforts of the legal staff of the FDA. In 1977, the FDA's Chief Counsel, Richard Merrill, instructed the US Federal Attorney in Chicago, Samuel Skinner (later to become Transportation Secretary and then Chief of Staff under President Bush) to convene a Grand Jury investigation into Searle and three of its senior officers for their wilful and knowing failure to make reports to the FDA, concealing material facts and making false statements in reports of animal studies conducted to establish the safety of the food additive, Aspartame.[21]

Early in 1977, however, Searle's firm of lawyers, Sidley and Austin invited Skinner to join their firm. Skinner accepted and placed the Aspartame case in the hands of subordinates, pending the appointment of a new Federal Attorney.[22] The case never met the deadline imposed by the US Statute of Limitations, despite repeated warnings from Richard Merrill at the FDA,[23] and the indictments were never filed.

The annual London Marathon is part-sponsored by NutraSweet which manufactures and markets Aspartame as a food additive. Such sponsorship associates NutraSweet in the public mind with fitness and health. Many believe that the controversy over the testing of Aspartame brings into question such an association.

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Lack of Oversight

Since the original investigations, a number of other tests have been conducted on Aspartame, many of which have provided results consistent with Aspartame being innocuous. Others, notably the studies of Professor John Olney and of Professor Richard Wurtman, have raised disturbing questions concerning Aspartame's short-term toxicity, particularly in relation to brain function.[24] Wurtman has produced both clinical and theoretical evidence that high doses of Aspartame may provoke epileptic seizures,[25] whilst Olney has raised the possibility that Aspartame may cause chronic brain damage, especially when consumed in combination with monosodium glutamate.[26] But despite such doubts over Aspartame's safety, the three pivotal tests on long-term toxicity, reviewed by the FDA's Bureau of Foods Task Force, have never been repeated.

In March 1990, I provided the UK government with a dossier of evidence showing that tests for the safety of Aspartame had not been properly conducted or reported and requested an urgent investigation, a matter which was later raised in the House of Commons.[27] I also provided copies of the dossier to the EC Commission's Scientific Committee for Food (SCF) in July 1990 and to the Joint Expert Committees on Food Additives (JECFA) of the World Health Organisation and the UN Food and Agriculture Organization in April 1991.

At the end of July 1992, the UK government announced the results of a review of the safety of artificial sweeteners, which reiterated their view that Aspartame, along with all other artificial sweeteners, is safe. Both the SCF and JECFA indicated that they too were satisfied that there was insufficient evidence to persuade them to reopen their evaluation of Aspartame.[28] Similarly, the JECFA and the FDA have indicated that they remained satisfied with the safety of Aspartame.

So far, none of these bodies has given a satisfactory explanation of their refusal to acknowledge that there are issues which need to be addressed. None of them has addressed or answered the allegations of irregularity in the conduct of the original tests. They have not cited, and apparently cannot cite, any subsequent laboratory studies that cover the disputed territory and which make up for the inadequacies revealed by Gross, Bressler and their colleagues in the FDA.

Vital Questions

The public cannot be certain that the tests to which Aspartame was subjected are adequate until the original tests have been physically repeated (rather than simply reviewed), preferably in independent laboratories. It is therefore difficult to avoid the conclusion that no one is in a position to judge properly the long-term health effects of Aspartame. The failure of the relevant authorities to address these matters in an adequate or open fashion raises vital questions which go far beyond this particular scandal.

It is possible that, after further research, Aspartame may be found to be safe beyond reasonable doubt, at least in respect of its putative embryotoxicity and carcinogenicity. But the shortcomings in the conduct of the regulatory authorities over such a long period remain to be fully investigated and explained, and steps must be taken to try to ensure that such shortcomings are not repeated. Until these matters are subjected to rigorous and open inquiry, food and chemical companies may assume that they can get away with poor research and incomplete disclosure. There is a danger that, as a result, seriously toxic chemicals or environmentally-destructive materials, will reach the market, with potentially disastrous consequences.

References

1. Aspartame is sold by other manufacturers under its chemical name.
2. FDA Searle Investigation Task Force, chaired by Carlton Sharp. *Final Report of Investigation of G.D. Searle Company*, 24 March 1976, pp.13-15.
3. Ibid., especially pp.1-7 and pp.13-16.
4. Bressler, J. et al., *Establishment Investigation Endorsements, of Searle Laboratories Division of G.D. Searle*, Chicago, for the US FDA Bureau of Foods, 18 July 1977 and 7 August 1977; and FDA Bureau of Foods Task Force Memo, *Authentication Review of Data in Reports Submitted to the FDA Concerning Aspartame, from the Bureau of Foods Task Force to Howard R. Roberts, Acting Director of Foods (HFF-1)*, 28 September 1977. H. R. Roberts, the primary recipient of this paradoxical document subsequently left the FDA and became the Director of the US Soft Drinks Association.
5. Bureau of Foods Task Force Memo, 28 September 1977, p. 3.
6. Bressler, J. et al., op. cit. 4, p.2.
7. Ibid., pp.2-8.
8. Ibid., pp.2-4.
9. Bureau of Foods Task Force Memo, 28 September 177, p.3.
10. Bressler, J. et al., op. cit. 4.
11. Personal communication, May 1987, from Dr Verrett. Those comments from Dr Verrett have been reiterated in a statement to a hearing on 3 November