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ADDITIVES: A GUIDE FOR EVERYONE

PENGUIN BOOKS

ABBREVIATIONS

ADI	acceptable daily intake of a chemical, measured in mg/kg bw
BIBRA	British Industrial Biological Research Association
Codex	Codex Alimentarius Commission
CoT	Committee on the Toxicity (of Chemicals in Food, Consumer Products and the Environment) at the DHSS
DHSS	Department of Health and Social Security
EEC	European Economic Community
FAC	Food Advisory Committee (of MAFF)
FACC	Food Additives and Contaminants Committee (of MAFF)
FAO	Food and Agriculture Organization (of the United Nations)
FDA	(the United States) Food and Drug Administration
FSC	Food Standards Committee (of MAFF)
GRAS	generally regarded as safe
JECFA	Joint Expert Committee on Food Additives
mg/kg bw	milligrams per kilogram of body weight of a laboratory animal or a human consumer
MAFF	Ministry of Agriculture, Fisheries and Food
NEL	no (observable adverse) effect level in laboratory animals, measured in mg/kg bw
ppm	parts per million
SCF	Scientific Committee for Food (of the EEC)
SF	safety factor
WHO	World Health Organization

Aspartame
also marketed under the names Nutrasweet and Canderel

Type This is a synthetic sweetener which is made by combining two amino acids L-phenylalanine and L-aspartic acid. It is almost 200 times as sweet as sucrose, but a lot more expensive.

Foods added to It can be found in no fewer than 125 different products but these are mainly confined to soft drinks and soft drink mixes and low-calorie yoghurts.

Toxicological evaluation and possible health hazards Since 1973, the controversy which has raged around Aspartame has exceeded those which have afflicted all other additives. On the face of it, we might expect Aspartame to be one of the least problematic chemicals. It is synthesized from a combination of two common, vital and naturally occurring amino acids. Amino acids are the fundamental constituents of proteins, and Aspartame is thought to be digested as a protein. There are, however, two central questions in the Aspartame controversy: first, has it been tested properly (even by the indifferent standards which currently prevail), and second, is Aspartame safe?

The production and sale of Aspartame are dominated by G. D. Searle & Co, which owns most of the crucial patents. Searle first petitioned the American government for permission to market Aspartame in 1973, but it was not until 1981 that the FDA permitted its commercial use, limiting it initially to dry food products. It was only in 1983 that the FDA finally approved its use in carbonated soft drinks, which is the major market. In October 1985 it emerged that G. D. Searle & Co had been acquired by the large chemical company Monsanto which, historically, had been one of the major manufacturers of Saccharin. Following their acquisition Monsanto detached the Aspartame business from the remainder of Searle and established the Nutrasweet Company.

In 1982 the FACC recommended that the use of Aspartame should be permitted in Britain, and Aspartame came on to the British market in September 1983. The major controversy over Aspartame has taken place in the USA, starting in 1973 and continuing for at least twelve years, but until 1983 the British press remained ignorant of, or indifferent to, the American debates. It has been only since 1983 that the significance of these important arguments has been appreciated by a handful of British commentators.

Searle first filed a petition with the FDA for permission to market Aspartame in 1973, and the FDA proposed to grant permission in 1974. Before the consequences of that decision could be implemented, objections were raised by independent scientists alleging that Aspartame causes mental retardation, brain lesions and neuroendocrine disorders. Before those issues could be resolved, a further complex set of objections was raised, the major of which concerned the fact that some scientists claimed that Searle had failed to conduct their safety tests properly, and their work had apparently been negligent.

The scandal was first uncovered by scientists from the FDA's drug control division. Dr Adrian Gross and his colleagues discovered, by examining carefully the laboratory records, that a large proportion of Searle's experimental work was profoundly unreliable. In response to these revelations the FDA established two Special Task Forces: one, under the auspices of the Bureau of Drugs, reviewed Searle's safety evaluations of their pharmaceutical products, while the second, under the Bureau of Foods, examined Aspartame.

The Aspartame Task Force had to institute careful reviews of as many as fifteen studies which were judged to be 'pivotal' in the sense of being integral to the approval of Aspartame. Their own internal review dealt with just three of these tests. Two concerned the potential embryotoxicity and teratogenicity in both rats and mice, while the third studied the carcinogenic potential to rats of a substance known as DKP (short for diketopiperazine), which is a breakdown product of Aspartame. The FDA decided not to rely entirely on their own resources to conduct all the reviews, and put pressure on Searle to oblige them to contract with the US Universities Association for Research and Evalution in Pathology (UAREP) to review and audit the validity of the remaining twelve sets of tests. Some commentators have argued that the members of the UAREP were not appropriately qualified to conduct the kind of investigation which was required, and consequently that their eventual conclusions cannot be considered to be reliable.

The results of the research by the Bureau of Foods Task Force make difficult but interesting reading. One of the central charges against Searle was that the conclusions of their tests, as described in the documents submitted to the FDA, failed to reflect accurately the raw data generated in the laboratories. The summaries, it was suggested, underestimated the possible toxicity of the chemical, and overestimated its safety when compared to the raw data. There were, moreover, '. . . significant deviations from acceptable procedures for conducting non-clinical laboratory studies'. It is especially ironic, therefore, that the Task Force Report seems to reproduce the mistake which it criticizes Searle for making. The conclusions of the Task Force Report fail accurately to reflect the information contained in the body of that report. It states that while these three tests were not properly conducted, and although there were marked differences between raw data and the summaries submitted in the petition to the FDA, these differences: '. . . were not of such a magnitude that they would significantly alter the conclusions of the studies'. The details of the Task Force Report, however, suggest precisely the opposite conclusion.

The Task Force had difficulty in evaluating the studies, in part because in some cases there just were no raw data with which to compare the supposed results. In other cases, it was impossible to determine which were the real raw results, and which were subsequent revisions or summaries. In some contexts, the Task Force had to rely on information and assumptions provided by Searle employees who had not been involved in the original work. At worst, it was impossible to identify the occasion on which a particular animal had died, for example, as the Report says: '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.' Most scientists do not believe in reincarnation, and we should not expect that the FDA or the FACC do so either.

When reviewing the test on DKP,

the Report lists no fewer than fifty-two major discrepancies in the Searle submission. One of the central problems concerned the quantities of DKP supposedly 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, was correct. It was impossible to reconcile the quantity of the chemical requisitioned from stores with the quantities supposedly fed to the animals. There were questions raised as to the extent to which the DKP was uniformly incorporated into the animals' food. There is clear evidence to show that the test substance was not properly ground, and inadequately mixed, so that it might have been possible for the animals to avoid the DKP while eating their food.

The disparity between the substance and the conclusion of the FDA Task Force Report is hard to understand. The investigators found so many mistakes which were of such a magnitude, and of such importance, that it would seem that no reliance can be placed on the results of these tests. The authors of the Report's conclusion, however, appear to have decided, perhaps for political reasons, to interpret the evidence 'generously', while the evidence invites or even demands a stricter assessment.

In 1978, the UAREP submitted its 1,062-page report, which concluded that the twelve studies they had audited were authentic. Despite the fact that these two reviews had concluded that Aspartame had been properly tested, and that the substance was safe, the objectors were still not satisfied, and furthermore a new complex set of objections to the safety of Aspartame were introduced. In an attempt to resolve the controversy once and for all, the FDA proposed the establishment of a so-called Public Board Of Inquiry (or PBOI). This was a unique institution; the procedure had never previously been used, and in all probability will not be used again.

The PBOI, which consisted of three academic scientists who were independent of both the FDA and Searle, were used as an alternative to the more usual formal evidential hearings, and were thought by some people to be better suited to dealing with the numerous scientific and technical complexities. The establishment of the Board was announced in June 1979, and they met early in 1980, publishing their conclusions in October 1980. They had two sets of issues on their agenda. On one of the crucial questions their view was that Aspartame consumption would not pose an increased risk of brain damage resulting in mental retardation, but on the other vital issue they concluded that the evidence available to them did not 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 testing.

In response, all the parties, namely G. D. Searle & Co, the Bureau of Foods, and the objectors, filed detailed exceptions to those parts of the Board's conclusions with which they disagreed. None the less, it was the responsibility of the Commissioner of the FDA to make a decision, for the Board's role was merely advisory and not decisive. In July 1981, the Commissioner, Arthur Hayes Jr, announced his decision to approve the use of Aspartame in food products other than soft drinks. In doing so he made it clear that he disagreed with the PBOI's interpretation of the issue concerning brain tumours. Hayes took the view that the available data were sufficient to persuade him that Aspartame does not cause brain tumours in laboratory animals. Subsequently, two of the three members of the Board have revised their own judgement and decided that they now agree with Hayes.

The issue is a rather subtle one; it concerns the way in which the experimental results are interpreted. The results of at least one experiment are very difficult to interpret. The reason for this is because the level of cancers in the concurrent control group of animals was unusually high. As a result, if one compares the results of the test group with concurrent controls then there is no statistically significant increase in cancer rates; whereas if one compares the test group with average historical control groups of the same types of animal, in similar tests, then one could conclude that there was a statistically significant increase in cancers.

This touches on a problem which affects large areas of toxicology, and is not confined either to tests for cancer or tests on Aspartame. The degree of variability in the background incidence of pathological symptoms in laboratory animals is vast, and poorly understood. In the toxicological literature there is extensive debate on whether the significant comparisons should be with concurrent controls or with historical averages, and the issue is unresolved, and probably unresolvable. In practice, we can find examples of firms and governments choosing comparisons with whichever groups yield the result which they wish to establish. In this case, Hayes and the FDA chose to accept the comparison between test animals and concurrent control, and in doing so were able to cite other examples of relatively high levels of cancer in animals not receiving test substances. I don't think that we can say who is right or wrong; what we can conclude, however, is that regulatory toxicology is too unreliable and too uncertain to enable us to be confident that the safety of Aspartame can be established.

JECFA first reviewed Aspartame in 1975. At that time their main doubts focused on the effects which DKP has produced in rats. Scientists had reported that in long-term feeding studies DKP had produced lesions in the uteruses of the rats. Despite detailed assistance from experts of the International Agency for Research on Cancer (IARC), JECFA were unable to decide on the character and significance of these lesions. They therefore postponed any decision until these matters had been clarified. They considered the subject again in 1978 by which time they had been reassured about the uterine lesions, but had become aware of (at least some of) the serious doubts about the validity of the toxicology data. JECFA therefore deferred any decision until they could be reassured about the validity of the data.

In 1980 they reported first that they had accepted the reassurances of the UAREP as to the validity of the tests, and second they produced a substantial and detailed report which reviewed eighty-one documents on Aspartame, seventy-nine of which were unpublished. JECFA established an ADI of 40mg/kg bw for Aspartame, but an ADI of 7.5mg/kg bw for

Aspartame's decay product DKP.

In 1982, Searle petitioned the FDA for permission to use Aspartame in carbonated soft drinks. The FDA again reviewed the controversial issues, but reconfirmed their interpretation of the evidence, and accordingly granted permission for this new use. In 1983 James Turner (a lawyer acting for the Community Nutrition Institute) and Dr John Olney (of Washington University, St Louis) again pressed the FDA to reconsider their decision. The FDA refused to do so, and in 1984 these objectors filed an appeal in the United States Court of Appeals to force the FDA to conduct formal hearings. In the autumn of 1985, three Appeal Court judges unanimously decided that the FDA had acted properly, and that the objectors had failed to show Aspartame to be unsafe. In spite of these institutional decisions, some scientists remain unconvinced both about the adequacy of these tests, and the interpretation of some of the results; and further lawsuits remain pending in US courts.

Searle's official position is that all their tests have been properly conducted, and that no charges have been preferred. In February 1986, however, US Senator Howard Metzenbaum published a thick dossier of documents which provided *prima facie* evidence that the reason why Searle had never been prosecuted was because their firm of lawyers had exercised undue influence over the Federal Attorney's office until the Statute of Limitations had expired and so ensured that no action could be taken.

Furthermore, in July 1986, the US General Accounting Office confirmed that Dr Arthur Hayes, who had approved Aspartame when FDA Commissioner, had accepted an appointment as a Senior Scientific Consultant to Burson-Marsteller two months after leaving the FDA. This is potentially significant because Burson-Marsteller have been acting as public relations consultants to Searle, but the report indicates that Hayes had not advised Searle before he joined the FDA, or after joining Burson-Marsteller.

This does not show that Aspartame is toxic, or that it was improperly approved, but it is hard to be confident on both counts, because much of the crucial evidence is unavailable. For example, although we do know that the information provided by Searle of both the US and UK governments did include a summary of the results of the three most controversial tests, it is impossible to discover the extent to which the British government, and its expert committees, knew about the doubts and uncertainties.

The consequence of all of these facts is that we cannot be certain that the tests to which Aspartame has been subjected are adequate, even by the relatively poor standards of current best practice, and so we cannot be confident that Aspartame is safe. The problem is made even more severe by the fact that there are some scientists who continue to argue that what we already know about Aspartame is sufficient to show that it is unsafe, at least for some consumers.

Two of the most persistent critics have been Professor John Olney and Professor Richard Wurtman (of the Massachusetts Institute of Technology). Wurtman has published a long series of papers reporting the results of his research on the safety of Aspartame, in which he has argued that serious problems exist. Apparently, Wurtman uses Aspartame himself, and considers it to be safe in low doses, but is worried about effects of consuming large amounts of Aspartame especially in combination with carbohydrates. Wurtman's research has been primarily concerned with the effects of consuming Aspartame on the biochemistry of the brain. He has argued that it may disturb brain functions in a complex variety of ways, which may provoke some severe and acute symptoms. In particular, Wurtman has argued that he has both theoretical and clinical evidence that very high doses of Aspartame can provoke epileptic seizures. Olney's research has concentrated, on the other hand, on the possibility that Aspartame might cause chronic brain damage especially when consumed in combination with Monosodium Glutamate (see 621), and he too remains dissatisfied about its safety.

Regulatory status Aspartame is permitted and used in the UK and USA, and although it is widely approved for use in table top sweeteners, it is not permitted for use in foods and/or beverages in Austria, Belgium, France, Greece, Italy, Holland or Portugal.

Hydrogenated Glucose Syrup

Type This is a complex mixture that is used as a sweetening agent. A range of products is available with this name and they vary from liquid syrups to crystalline solids. They are prepared by hydrolysing starches, that is to say using water and enzymes to get them to decompose. The intermediate product is then reacted with hydrogen to yield a mixture of maltitol and Sorbitol (see E420i) with other related compounds called polysaccharides. Weight for weight, it is not quite as sweet as sucrose, but it is cheaper, and some parts of the food industry are keen to use it as a substitute for glucose and sucrose.

Foods added to No specific uses have been reported.

Toxicological evaluation and possible health hazards Hydrogenated Glucose Syrup was first considered by JECFA in 1980. On that occasion they stated that they did not have sufficient information on its use or safety to permit an evaluation. In particular they noted the lack of adequate information on long-term and reproductive toxicity. In 1982 the FACC reported that the available evidence did not suggest that Hydrogenated Glucose Syrup was unsuitable for use in foods. Since they were satisfied that the Syrup was metabolized into glucose and Sorbitol, they did not insist on long-term tests. Since they had not completed their evaluation of Sorbitol, they listed Hydrogenated Glucose Syrup in Group B as temporarily acceptable pending further consideration. In 1983 JECFA reviewed the available data, mainly on metabolism and reproduction, and established a temporary ADI of 25mg/kg bw, but they still complained at the lack of adequate long-term data. The SCF reported their evaluation in 1985. They did not endorse the JECFA ADI, because they did not consider that the available evidence was sufficient. Although industry had supplied them with a lot of data, they considered much to be inadequate by modern standards. They approved the use of Hydrogenated Glucose Syrup, however, because they were satisfied that rats and humans metabolize it to glucose