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Ms Claudia Heppner
Head of EFSA "*Food Ingredients and Packaging*" Unit
Mr Georges Kass
Senior Scientific Officer, "*Food Ingredients and Packaging*" Unit
European Food Safety Authority
Via Carlo Magno 1A
43126 Parma
ITALY

Dear Ms Claudia Heppner & Mr Georges Kass

Re. DRAFT Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive

Further to my telephone conversations and email exchange with Christophe Wolff on 12th and 13th February, I am now sending you this letter as my detailed response to the EFSA Panel's *DRAFT Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive*, which was issued on 8th January 2013.

I would be pleased to travel to EFSA in Parma to discuss the issues raised in my response, or to meet EFSA colleagues at a suitable agreed location, such as in Brussels.

I look forward to receiving a detailed response to these comments, especially in the light of the failure of the January draft to address the issues raised by the dossier of 30 documents that I delivered to EFSA in Autumn 2011, in response to an explicit request from EFSA.

My detailed comments begin on the next page.

Yours sincerely

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Ccs including: Kartika Liotard MEP, Corinne Le Page MEP, Ms Sue Davies Which & EFSA Board; Alisdair Wotherspoon UK FSA; Jan Marco Mueller European Commission; Caroline Lucas MP

EFSA on Aspartame January 2013
a lost, but not the last, opportunity

Executive summary

The draft report on the safety of aspartame, issued by the European Food Safety Authority's ANS panel on 8 January 2013, is deeply flawed.

There are at least two main types of flaws: those arising from the criteria by which 'evidence' has been selected, and those arising from the criteria by which those studies are interpreted.

The criteria of inclusion have been overly narrow, and have in particular excluded vital documents that bear directly on the scientific competence with which some pivotal studies were conducting and on the accuracy with which they were reported. Such documentary evidence is directly relevant to the reliability of the reported data, and on the truth of the claims based on those studies.

The implicit criteria of interpretation of the studies that have been included are perverse and biased. The panel could only have reached its conclusion that aspartame is safe by implicitly assuming that almost all studies indicating no adverse effects are entirely reliable, even though they have numerous weaknesses and were almost all commercially funded, while all the studies indicating that aspartame may be unsafe are deemed unreliable, even though they sometimes have particular methodological strengths and even though they have all been funded independently of vested commercial interests.

On each of the 80 occasions when the panel discusses a study that indicated no apparent risks from aspartame those studies are taken at face value and typically assumed to be reliable. However, on each of the 27 occasions when the panel discusses studies that indicate that aspartame may pose risks, the panel is unremittingly critical of them, implicitly assuming that they must be misleading, so dismissing them. Often those worrying studies are dismissed not because of evidence but on flimsy grounds, for example by invoking speculative hypotheses without supporting evidence.

The panel reached its conclusion that aspartame is safe not by applying uniformly critical standards to all the evidence from all studies, but by routinely forgiving the shortcomings of favourable studies yet being unremitting critical of all the studies suggesting any possible risks. The panel's overall conclusions is driven more by the panel's biased assumptions than by the evidence adduced.

One possible explanation for the asymmetric bias in the interpretation of studies might be found in the pattern of conflicts of interest that characterise the members of the panel. Of the 17 members of the EFSA panel, 7 have direct commercial

conflicts of interest, and another 5 have institutional conflicts of interest – for example because their employers have already announced that aspartame is safe. Only 4 panel members are not characterised by some relevant conflicts of interest.

EFSA should therefore discount the draft report, convene a new panel composed only of, and supported only by, experts who are free of any conflicts of interest. They should be asked to review all the evidence, not just some of it. They should also make explicit their criteria of interpretation, and then show that those criteria have been consistently applied, and they should be applied to prioritises the protection of consumer and public health over commercial or industrial considerations. The European Commission and the European Parliament should also take responsibility for ensuring that EFSA acts properly to protect consumers rather than assisting the food and chemical industries.

EFSA on Aspartame January 2013
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Introduction

The EFSA website http://www.efsa.europa.eu/en/consultations/call/130108.htm asserts that the:

> …EFSA's Panel on Food Additives and Nutrient Sources added to Food (ANS) has launched an open consultation on a draft opinion on the re-evaluation of aspartame (E951). This document is the first full evaluation of aspartame that has been requested of EFSA. The ANS Panel has taken all available information including new human safety data into consideration, and the draft opinion addresses the potential safety concerns related to toxicity carcinogenicity and genotoxicity as well as possible reproductive and developmental effects related to aspartame and its metabolites and breakdown products.

The claim that all available information has been taken into considerations is seriously misleading. Evidence that available and directly relevant information has not been taken into consideration is provided by the dossier of documents that I delivered to EFSA in the autumn of 2011.

The ANS Panel's criteria of inclusion of relevant evidence

I responded to EFSA's initial call, on 1 June 2011, for data on Aspartame with an annotated list of 30 documents on 26 July 2011. I selected those documents from my extensive collection of material on the aspartame saga because I judge them to be indispensable for any competent, adequate and robust assessment of the safety of aspartame. In that submission I explained that the documents comprising my dossier indicate that:

1. when aspartame was initially tested by, and for, G D Searle in the 1970s, several of the pivotal tests were incompetently conducted and misleadingly reported. Furthermore, when a senior US FDA toxicologist uncovered the problems, and they were then investigated by FDA task forces, further evidence emerged indicating that no reliance could be placed on the supposed results of those test.

2. The dossier of 30 documents reveals that in response Searle, and then Nutrasweet, went to considerable lengths to conceal, or down-play the significance of, those short-comings in the testing and reporting. Those tactics have however not obliterated evidence, even though the ANS panel failed top engage with it.

EFSA replied to my letter of 1st June on 14th October 2011, requesting electronic copies of most of the documents listed in my dossier. As the dossier was too large to be sent by email, at 38 Mbs, I burned it onto a CD-Rom and dispatched it to EFSA. I received email confirmation of its arrival on 4th November 2011 from a Senior Administrative Assistant, EFSA ANS Panel.

The ANS panel only refers to 4 of the 30 documents of which my dossier was composed, and even then it fails to addresses their clearest implications. The panel does comment on the studies conducted by the Ramazzini Foundation (cf Item 28) and a document referred to in my dossier as Item 15, and as the UAREP report, where that abbreviation stands for Universities Association for Research and Evaluation in Pathology – which is referred to by the EFSA Panel as 'the authentication review of selected materials submitted to the Food and Drug Administration' – and on page 145 as E102a, E102b and E102c . Otherwise the EFSA Panel fails to refer to, or take any account of, my dossier or the documents of which it is comprised. A list of the documents comprising my dossier of July 2011 is provided in Appendix 1.

Curiously the ANS panel's draft states: "The Panel was not provided with a newly submitted dossier and based its evaluation on previous evaluations, additional literature that became available between then and the end of November 2012 and the data submitted following a public call for data." (page 3 lines 42-44) That text suggests that the panel only counted documents submitted by the companies that manufacture aspartame as constituting a 'dossier', while discounting or ignoring the dossier that I provided. Even though the documents comprising my dossier entail that no reliance can be placed on the results of at least 15 studies, all of which have been accepted for and reviewed by the ANS panel.

While the documents in my dossier are not themselves reports of laboratory experiments, they frequently refer directly to reports of laboratory experiments, and are directly relevant to the truth of claims about those studies that purport to be scientific. The document in my dossier also provide show that considerable efforts were invested by G D Searle and others into covering-up evidence of the failings of the original 15+ studies.

The EFSA website at http://www.efsa.europa.eu/en/consultations/call/130108.htm claims that the draft has included 'scientific' data, but it fails to clarify where it draws the scope and limits of that term.

The panel's draft states (page 14 lines 506-512):

> "The Panel was not provided with a newly submitted dossier and based its evaluation on previous evaluations, additional literature that became available between then and the end of November 2012 and the data submitted following a public call for data. The selection criteria for scientific data consideration for the re-evaluation of aspartame described in this opinion applied to both the existing

published and unpublished scientific literature. These criteria were agreed at the 28th Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) Plenary meeting on 25-27 October 2011 and were published with the minutes of that meeting. These criteria are reproduced in Annex A."

The text of the panel's Appendix A states:

SELECTION CRITERIA FOR SCIENTIFIC DATA CONSIDERATION FOR THE RE-EVALUATION OF ASPARTAME

The selection criteria for scientific data consideration for the re-evaluation of aspartame described in this report will be applied to the existing published and unpublished scientific literature. The literature database will include scientific peer reviewed papers and relevant non-peer reviewed papers (such as technical reports and published conference proceedings) identified through exhaustive literature searches performed using commercial databases and providers (e.g. ISI Web of Knowledge, PubMed), available from previous evaluations by EFSA and SCF or obtained as a result or EFSA's recent public call for scientific data on aspartame (closure: 30 September 2011).

Types of studies that will be considered within the criteria for inclusion in the selection process.

a) Experimental studies
b) Epidemiological studies in humans
c) Case reports supported by medical evidence

Table 1: Source and Type of information available that may fall in these categories:

Peer-reviewed	Not peer-reviewed
Published papers	Unpublished study reports
Meeting abstracts (conference proceedings)	Papers in non-peer reviewed journals or non-peer reviewed e-papers
Published case reports	Meeting abstracts
	Case reports in non-peer reviewed journals

Tiered Approach for the Selection Process

Tier 1. Criteria to be used for the inclusion of scientific papers and reports in the selection process:

1. All studies provided by the applicants (including unpublished study reports non peer reviewed) with the original application dossier.
2. All studies on the safety and use of aspartame commissioned by national authorities.

3. Papers and reports that have been subject to an independent scientific peer-review process (i.e. process that scientific journals use to ensure that the articles to be published represent the best scholarship available in terms of solid scientific soundness and quality control) and have been subsequently published in a scientific journal.
4. For non independently peer reviewed papers and reports assessment based on the quality control procedures applied and the study designs used with reference to validated standards (e.g. OECD protocols and GLP Guidelines).

Tier 2. Criteria to be used for the rejection of papers and reports in the selection process:

1. Insufficient details provided on the performance or outcome of the studies (EFSA, 2009).
2. Insufficient information to assess the methodological quality of the studies (EFSA, 2009).

References

EFSA, 2009. *Guidance of the Scientific Committee on transparency in the scientific aspects of risk assessments carried out by EFSA. Part 2: General principles*. The EFSA Journal 1051, 1-22.

The panel indicates that it deems any and all dossiers and studies submitted by the [original] 'applicants' and within the scope of this review, but a dossier submitted by someone, such as myself, who is not an industrial or commercial applicant is not anywhere acknowledged or listed within the draft. More importantly, its analysis and implications has been ignored.

The panel's claim that "All studies on the safety and use of aspartame commissioned by national authorities..." have been included is misleading. Many of the documents in my dossier satisfy that description, but have not been included. In the USA, where the Constitution stipulates that the US government consists of three branches, namely the Executive, the Legislative and the Judicial branches, documents having a direct bearing on the safety of aspartame from either the Executive and the Legislative branches should be satisfy this criterion. None the less, at least 15 of the document from my dossier satisfy that criterion, but have not been taken into account. Those documents include items: 3, 4, 5, 21, 22 and 25 from Congress and items 7, 8, 9, 10, 12, 13, 14, 16, 18 and 19 from the Executive branch.

In any case the criteria of inclusion should have been wide enough to encompass any and all documents, from whatever source, that are relevant to an adjudication of the safety of aspartame. Sadly that has not been the case, and that is reason enough for those extra items to be included.

In practice however the panel has adopted an interpretation of 'scientific' evidence that is too narrow. It is narrow as it only includes evidence purporting directly to report the conduct and results of laboratory experiments. It is too narrow because it fails to include evidence about the ways in which many of those experiments were conducted and reported. It is also consequently complacent as it often takes reports of experiments at face value, as if they had been competently conducted and accurately reported, despite the fact that I had provided EFSA with detailed documentary evidence showing that at least 15 of those studies had previously been discredited, and rightly so. If the documents that I submitted had taken into consideration and proper account, then a rather different conclusion would have resulted.

The list of studies that were deemed 'pivotal' by the FDA to the safety of aspartame, and which were discredited by the investigations of the US FDA's Task Forces included 15 studies, that are referred to by their code numbers, which have been used both by Searle, Monsanto, Nutrasweet and by EFSA. They include 3 reviewed by the team lead by Bressler and then by the Bureau of Foods Task Force, namely:

E-5
E-77/78
E-89

Those that were reviewed by the UAREP, were:

E-9
E-11
E-19
E-28
E-33/34
E-70
E-75/76
E-86/87
E-88
E-90

Nonetheless, every one of those studies has been included in the scope of EFSA's panel's draft report. For the purposes of the panel's draft, they are all deemed to be 'scientific', and so included, while the documents providing detailed evidence that they were based on poorly conducted experimental work, which was not accurately reported, are in effect not deemed to satisfy the EFSA panel's narrow criteria for being 'scientific'.

To explain why none of the studies listed immediately above should have been taken at face value, and why no reliance can or should be placed on their reports, it is necessary to set out an historical narrative that derives in large part from the documents of which my dossier submitted to EFSA was composed.

Key highlights from the history of the testing and regulatory review of aspartame:

US pharmaceutical company G D Searle first filed a petition with the US FDA for permission to market Aspartame in 1973, and the FDA initially proposed to grant permission in 1974. Before the consequences of that decision could be implemented, however, objections were raised by independent scientists alleging that aspartame could cause mental retardation, brain lesions and neuroendocrine disorders.[1] Before those issues could be resolved, a further complex set of objections were raised, the most important of which concerned the fact that some scientists claimed that Searle had failed to conduct their safety tests properly, and that the laboratory work had been incompetent.

The shortcomings in the testing and reporting of studies on aspartame were first uncovered by scientists from the FDA's drugs division. Dr. Adrian Gross and his colleagues discovered, by examining carefully G D Searle's laboratory records, that a large proportion of Searle's experimental work was profoundly unreliable.[2] In response to those 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.[3]

The Bureau of Foods Task Force had to institute careful reviews of 15 studies that were judged to be 'pivotal' in the sense of being integral to the approval of Aspartame. The FDA's own internal review dealt with just three of these studies. 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.[4] The FDA claimed it was unable to conduct all the reviews because of resource limitations, and so put pressure on Searle to oblige them to contract with the organisation known as 'the US Universities Association for Research and

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[1] McCann J.E., (1990) *Sweet Success: How Nutrasweet Created a Billion Dollar Business*, Business One Irwin, Homewood, Illinois, Ch. 2

[2] US Senate, *Preclinical and Clincal Testing by the Pharmaceutical Industry*, Joint Hearings before the Sub-Committee on Health of the Committee on Labor and Public Welfare and the Sub-Committee on Administrative Practice and Procedure of the Senate Judiciary Committee, Part III, Tuesday April 8th 1976, see esp. pp. 1-20

[3] FDA *Memorandum to Searle Investigation Steering Committee from the Searle Investigation Task Force, Final Report of Investigation of G.D. Searle Company*, 24 March 1976

[4] Bressler J et al, *Establishment Investigation Endorsements, of Searle Laboratories Division of G.D. Searle, Chicago, for the Bureau of Foods*, 18th July 1977 and 7th August 1977

Evaluation in Pathology' (or UAREP) to review and audit the validity of the remaining 12 sets of tests.[5]

The FDA's decision to outsource that work to the UAREP was puzzling, because the FDA had just received a fresh *tranche* of funding from Congress, following the Senate Committee hearings in April 8th 1976, to enable it more fully to scrutinize toxicological data from the chemical industry. More, Adrian Gross 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 the UAREP did not possess the requisite expertise to rule upon the conduct of animal experiments.[6] Gross considered that the main problem lay in the manner in which the studies had been conducted, yet the 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. In the event, the UAREP restricted its review to a consideration of the interpretation of pathological samples mounted onto glass slides, and examined under microscopes, while ignoring or neglecting the prior activities that had resulted in those tissue samples being located on those slides. Unfortunately the problems were primarily located in those prior activities, but they were outside the scope and competence of the UAREP team.

The EFSA panel does provide some discussion of the UAREP report, in the very final section namely Annex L, which is on pages 243-5, lines 6935-7047. The text provided in the draft is at a crucial point ungrammatical and unclear. A crucial sentence is in lines 7007-9: "Overall, UAREP has interpreted the results only to the experiments as designed, it has addressed itself to the question of whether the experiments were carried out according to protocol plans and the accuracy and reliability with which the experiments were performed and reported to the FDA."

Given that the panel correctly states that the "…UAREP has interpreted the results only to the experiments as designed…" it appears that the next clause is missing one crucial word, namely 'not', so that it should read: "…it has [not] addressed itself to the question of whether the experiments were carried out according to protocol plans and the accuracy and reliability with which the experiments were performed and reported to the FDA." In the correspondence between Gross and one of his superiors, Carlton Sharp, dated 4 November 1976 (Item 9 in my dossier of autumn 2011) Gross draws attention to that probable outcome. Gross's initial expectations and retrospective comments on the report from the UAREP[7] confirm that the UAREP was not expected to, and in the event did not, '…addressed itself to the question of whether the experiments were carried out according to protocol

[5] Gross A. 'Letter to Senator Howard Metzenbaum from Dr Adrian Gross', October 30th 1987, reproduced in *"Nutrasweet" - Health and Safety Concerns, Hearing before the Committee on Labor and Human Resources of the US Senate*, 3rd November 1987, pp. 430-439

[6] Gross A, Letter from Dr Adrian Gross to Mr. Carl Sharp at the Food and Drug Administration, 4th November 1976, reproduced in *"Nutrasweet" - Health and Safety Concerns, Hearing before the Committee on Labor and Human Resources of the US Senate*, 3rd November 1987, pp. 440-44

[7] Two letters from Dr Adrian Gross to Senator Howard Metzenbaum, both dated 3 November 1987, and reproduced in the record of US Senate Committee on Labor and Human Resources

plans…' not did the UAREP consider '…the accuracy and reliability with which the experiments were performed and reported to the FDA.' For those reasons, the judgement of the UAREP cannot, and so should not, be interpreted as having 'authenticated' the reports of those 12 studies.

The results of the research by the Bureau of Foods Task Force make puzzling but interesting reading.[8] One of the central allegations against Searle was that the conclusions of their tests, as described in the documents submitted to the FDA, failed accurately to reflect the raw data generated in the laboratories. The summaries, it was argued, underestimated the possible toxicity of the chemical, and its breakdown products such as DKP, and overestimated its safety when compared to the raw data. There were, moreover, "...significant deviations from acceptable procedures for conducting non-clinical laboratory studies."[9]

It is puzzling, therefore, that the Task Force Report occasionally seems to reproduce the mistake for which it criticises Searle. The conclusions of the Task Force Report fail fully to reflect the information contained in the body of that report. It states that while these 3 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."[10] The details of the Task Force Report, however, derive from the Bressler Report suggest precisely the opposite conclusion.[11]

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, as the Task Force explained, it was impossible to determine which the real raw results were, and which were subsequent revisions or summaries. In some contexts, the Bressler team and the Bureau of Foods 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 animals had died, for example, as the 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."[12] Most scientists do not believe in reincarnation, and we should not expect that the EFSA panel would do so either.

When reviewing the test on DKP, the Report lists no fewer than 52 major discrepancies in the Searle submission.[13] One of the central problems concerned

[8] US FDA Bureau of Foods Task Force, *Authentication Review of Data in Reports Submitted to the FDA Concerning Aspartame*, FDA Memo from the Bureau of Foods Task Force to Howard R. Roberts, Acting Director of Foods (HFF-1), 28th September 1977
[9] Bureau of Foods Task Force 1977, p. 3
[10] Bureau of Foods Task Force Report, 1977
[11] Bressler et al 1977
[12] Bressler et al 7 Aug 1977 p. 2
[13] Bressler et al, op cit pp. 2-8

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 photographic 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.[14]

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 implies that no reliance could be placed on the reports 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 May 1987 I contacted Dr Jacqueline Verrett, one of the members of the Bureau of Foods Task Force, seeking an explanation. She provided the following statement on the record:

> "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 that 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. Our remit was limited to a comparison of the Bressler data against the original data. 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." (Emphasis added)

Those comments from Jacqueline Verrett were reiterated in her statement at the hearing on 3rd November 1987 of the US Senate Committee on Labor and Human Resources.[15]

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[14] Bressler et al op cit pp. 3-4

[15] US Senate Committee on Labor and Human Resources, 3rd November 1987, item 24, pp. 383-390

In 1978, the UAREP submitted its 1062-page report, which concluded that the 12 studies it had audited were 'authentic'.[16] The limited competence, scope and content of the UAREP report should not therefore be interpreted as having certified the competence of the 12 studies it had reviewed. That is, however precisely the manner in which the EFSA panel has interpreted it. (page 68, lines 2172-74)

Despite the fact that the Bureau of Foods Task Force and UAREP reviews had been contrived to suggest that Aspartame had been properly tested, and that the substance is safe, well-informed objectors were still not satisfied, and furthermore a new complex set of objections to the safety of Aspartame were introduced.[17]

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).[18] This was a unique institution; the procedure had never previously been used, and in all probability will not be used again.[19] The PBOI, which consisted of three academic scientists who were independent of both the FDA and Searle, was used as an alternative to the more usual formal evidential hearings, and was 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 it met early in 1980, publishing its conclusions in October 1980.[20] 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 of 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. Nonetheless, 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

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[16] UAREP, *Authentication Review of Selected Materials Submitted to the Food and Drug Administration Relative to Application of Searle Laboratories to Market Aspartame*, Universities Associated for Research and Education in Pathology Inc., 18th November 1978

[17] Graves F, 'How Safe Is Your Diet Soft Drink?', *Common Cause*, July/August 1984, pp. 25-43; McCann J E, *Sweet Success: How Nutrasweet Created a Billion Dollar Business*, Business One Irwin, Homewood, Illinois, 1990, pp. 37-48

[18] Brannigan V, 1983, 'The First FDA Public Board of Inquiry: The Aspartame Case', Chapter 9 in *Law and Science in Collaboration*, Nyhart JD & Carrow MM (eds), Lexington Books, Mass.

[19] Smyth TR, 1983, 'The FDA's Public Board of Inquiry and the Aspartame Decision', *Indiana Law Journal*, Vol. 58 pp. 627-649

[20] US FDA, *Report of the Public Board of Inquiry into Aspartame*, 1980

than soft drinks.[21] 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.

In July 1986, the US General Accounting Office confirmed that Arthur Hull Hayes, who had approved Aspartame when FDA Commissioner, had subsequently accepted an appointment as a Senior Scientific Consultant to Burson-Marsteller two months after leaving the FDA. (GAO 1986) This is relevant because Burson-Marsteller has acted as public relations representatives for G D Searle and Nutrasweet, but the GOA report states that Hayes had not advised Searle before he joined the FDA, or after joining Burson-Marsteller.

GD Searle's official position, and subsequently that of Monsanto, Nutrasweet and Ajinomoto too, has been that all the tests were properly conducted, and that no charges were preferred against Searle in relation to Aspartame. In February 1986, however, US Senator Howard Metzenbaum published a 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 US Federal Attorney's office in Chicago until the Statute of Limitations had expired and so ensured that no action could be taken.[22] The evidence adduced by Metzenbaum included a letter from the US FDA's Chief Counsel Richard Merrill, which is document 10 in my dossier, in which Merrill summarises some of the most salient facts that he deemed sufficient for a criminal indictment.

The first paragraph of the front page of that letter is reproduced below:

[21] *Federal Register*, Friday July 24, 1981, Part IV, Department of Health and Human Services, Food and Drug Administration, Aspartame; *Commisioner's Final Decision, Docket* No. 75F-0355, pp. 38284-38308

[22] Metzenbaum H, Dossier of 30 documents released by Senator Howard Metzenbaum, Washington DC, US Senate 6.30pm EST, 6th February 1986

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
ROCKVILLE, MD. 20852

January 10, 1977

OFFICE OF THE GENERAL COUNSEL

Honorable Samuel K. Skinner
United States Attorney
Northern District of Illinois
219 South Dearborn Street
Room 1500 South
Chicago, Illinois 60604

Dear Mr. Skinner:

We request that your office convene a Grand Jury investigation into apparent violations of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 331(e), and the False Reports to the Government Act, 18 U.S.C. 1001, by G. D. Searle and Company and three of its responsible officers for their willful and knowing failure to make reports to the Food and Drug Administration required by the Act, 21 U.S.C. 355(i), and for concealing material facts and making false statements in reports of animal studies conducted to establish the safety of the drug Aldactone and the food additive Aspartame. Concealing material facts relative to the Aldactone study also resulted in that drug being misbranded within the meaning of 21 U.S.C. 352(a) and 321(n), in violation of 21 U.S.C. 331(a).

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In his role as FDA Chief Counsel, Richard Merrill was therefore satisfied that the FDA had gathered sufficient evidence for G D Searle to be indicted for:

> "…violations of the federal Food, Drugs and Cosmetics Act…and the False Reports to the Government Act…and for concealing material facts and making false statements in reports of animal studies conducted to establish the safety of…the food additive Aspartame."

The dossier published by Metzenbaum in 1986 also included documents showing that the firm of lawyers who represented Searle, Sidley & Austin, repeatedly invited firstly Samuel K Skinner, the recipient of Merrill's letter, as well as the next two Chicago-based Federal Attorneys that were responsible for acting on Merrill's request to convene a Grand Jury to be convened to indict Searle, until the statute of limitation had expired. That implies that the fact that Searle was not indicted should not be interpreted as if it showed that Searle had no case to answer or that Searle did not deserve to be indicted.

My dossier of 30 documents, delivered to EFSA in the autumn of 2011, was intended to provide EFSA with an opportunity to grasp the structure and some of the details of that chronological saga, but the EFSA draft indicates that those critical facts have either not been grasped or, for reasons that remain to be explained, the EFSA panel and/or its secretariat have chosen to discount or ignore those facts and the documents comprising the dossier I provided.

The way in which the panel interprets its criteria of selection of studies for inclusion in, and exclusion from, this draft, reveal a predominantly narrow interpretation of which evidence is deemed 'scientific', there is one conspicuous exception to the narrow focus on results from laboratory experiments. The panel includes and comments enthusiastically on just one review article, but no other, and the panel fails to explain its inclusion.

That review paper, by Magnuson et al, 2007[23] focussed on: "…the neurotoxicity of aspartame……" (page 84, line 2964) One of the several matters that the EFSA panel failed to acknowledge is that several of the authors of that review had commercial links to companies that produce or use aspartame. The panel comments (page 84 lines 2969- 2973) that the conclusions of the review by Magnuson et al were subsequently endorsed by an EFSA Advisory Forum. The panel also neglects to acknowledge that members of that particular forum also included individuals with commercial conflicts of interest. Those facts increase the importance of the question as to why that review article received preferential treatment not granted to any other reviews? It also highlights the more general problem that the panel paid no attention to potential conflicts of interest amongst the authors whose work is discussed.

The issue of conflicts of interest will be addressed in more detail towards the end of this document; the next section focuses on how the EFSA panel interpreted the data from those studies that were included in its draft.

[23] Magnuson BA, Burdock GA, Doull J, Kroes, RM, Marsh GM, Pariza MW, Spencer PS, Waddell WJ, Walker R and Williams GM, 'Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies'. *Critical Reviews in Toxicology*, 2007, 37, pp 629-727

The panel's criteria of interpretation: both explicit and implicit

This section focuses of the ways in which the panel has chosen to represent and interpret information, data and results from the studies that have been included. If more time had been available between the publication of the draft and the target date for submitting responses, this document would have commented in detail on more than just Section 3, which focuses on the **Biological and toxicological data of aspartame**, but only that section will be discussed here.

While the putative toxicity of aspartame's breakdown products, such as methanol and DKP, are important, constraints of time have precluded a comprehensive discussion of Sections 4 – 13, but Section 3 is pivotal, as it focuses specifically on aspartame. It would however be surprising if the pattern found in Section 3 were not also to be found in those sections.

The discussion in this section will highlight particular studies referred to by the panel in Section 3, and in each case it will identify the way in which the panel portrays the findings of those studies, and the ways in which it chose to interpret the data, and the reasons given. The reasons that the panel provide constitute its explicit criteria of interpretation of evidence. This discussion will frequently draw attention to that the fact that reasons given are not sufficient to explain the panel's interpretations, and will identify key assumptions made by the panel that, although they remained implicit and unacknowledged, are necessary to explain the panel's chosen interpretations.

Toxicologists and statisticians have together developed a useful vocabulary, which will be used to simplify the following discussion, and diminish the repetition of qualifying sub-clauses. From toxicologists we take the contrast between what is often referred to as 'positive' and 'negative' results. In the terminology of toxicologists, the results of a study are 'positive' if the evidence indicates the presence of an adverse effect. Correspondingly, results are deemed as 'negative' if the evidence does not indicate the occurrence of any adverse effects.

Statisticians have introduced a useful vocabulary used to refer to the possible imprecision in the results of studies. Statisticians routinely refer to two main types of errors: those termed a 'false positive' and those referred to as a 'false negative'. When applied to the results of toxicology tests, a 'false positive' arises when a study appears to show a risk, although in truth no such risk arises. Correspondingly, a 'false negative' arises when a study fails to show a risk when in truth there is such a risk.

Summarising much of the following discussion using those terms, it will show that the panel interprets almost every apparently negative study to be a true negative, and every single apparently positive finding to be a false positive. When the panel discusses its interpretations of the apparent findings of studies, it seems endlessly

alert for possible false positives, while being almost entirely blind to possible false negatives. In that sense, the panel's criteria of interpretation are asymmetric, and that asymmetry constitutes an unscientific and unacceptable bias.

Rather than exhaustively identifying every one of at least 80 occasions on which the panel treats an apparent negative as if a true negative, a few exceptions will be highlighted, namely those occasions when apparently negative studies are discounted as insufficiently reliable. On the other hand the discussion will specifically identify and discuss each of the 27 occasions when apparent 'positives' are critiqued, discounted or rejected as failing to show any such risk.

That analysis will be supplemented, moreover, with the observation that 100% of commercially-funded studies provide apparently 'negative' findings, whereas 100% of the studies that suggest 'positive' findings have been funded by independent non-commercial sources. It will be argued, furthermore, that that remarkably close correlation is not accidental, but systemic. To reach its conclusion that aspartame is unproblematically safe, it was therefore necessary for the panel to assume that all apparently negative studies are unproblematically reliable, even though they have almost always been commercially-funded, while all apparently positive studies are false positives, though they have all been independently funded.

The following discussion examines each of the occasions at which the panel rejected an apparent 'positive' and does so in the sequence in which they are discussed in the EFSA draft.

1. In 1996 Olney and his colleagues published a paper[24] that reported epidemiological evidence that suggested that the introduction of aspartame to the USA may have been responsible for an abrupt and significant increase in the incidence of a particularly aggressive type of brain tumour, called glioblastomas. Their argument was reinforced by two separate considerations. One was that an early, but flawed Searle-sponsored, study conducted with monkeys had produced evidence suggesting a link between aspartame consumption and blastomas.[25] Secondly there was some biochemical evidence indicating a mechanism through which aspartame could exert a carcinogenic effect namely as a consequence of a chemical reaction known as 'nitrosation'.[26] Predictably, shortly after publication, the US FDA and the US food and chemical industries discounted his analysis.

[24] Olney JW, Farber NB, Spitznagel E and Robins LN, 1996 'Increasing brain tumor rates: is there a link to aspartame?' Journal of Neuropathology and Experimental Neurology, 1996, Vol 55, 1115-1123

[25] K. S. Rao, R. G. Mc Connell, and H. A. Waisman, *52 Week Oral Toxicity Study In The Infant Monkey* 10 October 1972

[26] Meier I, Shephard SE and Lutz WK, 1990. 'Nitrosation of aspartic acid, aspartame, and glycine ethylester. Alkylation of 4-(p-nitrobenzyl)pyridine (NBP) in vitro and binding to DNA in the rat', Mutation Research, 1990, 238, pp 193-201; Shephard SE, Wakabayashi K and Nagao M,

In the UK and Europe it was officially discounted because similar patterns had not emerged in their local data, but that may well have been because the age-profile of people consuming aspartame sweetened products differs between the USA and this side of the Atlantic. In the UK and continental Europe, artificially sweetened products are predominantly consumed by younger people rather than by 'senior citizens', while it was the latter group that Olney argued were especially at risk.

The response of the panel to those claims is as follows:

> "The conclusions of this epidemiological study have been criticised by a number of scientists who questioned the methodology used and the interpretation of the data…The SCF considered this report at its 107th meeting in June 1997 and concluded that the data did not support the proposed biphasic increase in the incidence of brain tumours…The issue has also been considered by the FDA and by the UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment…The FDA stated that analysis of the National Cancer Institute database on cancer incidence in the USA did not support an association between the use of aspartame and increased incidence of brain tumours… The COC agreed that the findings provided no evidence for the proposed biphasic increase in the incidence of either all brain tumours or selected tumour types in the USA during the 1980's and concluded that the data published by Olney *et al.* (1996) did not raise any concerns about the use of aspartame in the UK...."[27]

In other words, without adding to the judgements of others, the panel simply accepted the judgements of other official bodies (the US FDA, the SCF and the UK's CoC). In acquiescing with those previous criticisms of Olney and colleagues' arguments the panel failed to take account of the fact that before each of those bodies had reviewed and commenting on Olney's paper, they had previously asserted that aspartame was entirely safe. If they had accepted Olney's arguments they would have been repudiating the scientific policy positions of the institutions in which they were employed; and it takes far more courage to question the safety of a product once it has already been approved than before its use is authorised.

2. In the middle years of the first decade of this century researchers at the Ramazzini Foundation in Bologna, Italy started to publish the results of their work, which are the only independently-funded long-term animal carcinogenicity studies of aspartame. Results from a rat feeding study began to emerge in 2005 in

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'Mutagenic activity of peptides and the artificial sweetener aspartame after nitrosation', *Food and Chemical Toxicology*, 1993, 31, 323-329

[27] EFSA Draft January 2013, page 34 lines 837-849

the work of Belpoggi et al[28] and by Soffritti and colleagues in 2006[29]. The resuilts of a similar study on mice emerged a few years later.

The Ramazinni Foundation, which one of the very few toxicology testing laboratories in Europe that is independent of commercial organisations, performed what it described as:

> "...a mega-experiment using 7 groups of Sprague-Dawley rats (100-150/sex/group), treated with APM in feed at various dose levels (including one very close to the ADI for humans), from 8 weeks of age until natural death."[30]

The conventional protocols for long-term rodent feeding studies typically involve feeding test compounds to four groups of animal, with 50 males and 50 females in a low-dose, a mid-dose and a high-dose groups as well as the corresponding control group, making a total of 400 animals. Moreover, customary practice often involves killing the animals when they are some two and a half years old, ie at 30 months. The Ramazzini studies therefore differed from customary practices by using a total of 1,800 rats (900 males and 900 females) and testing them with 6 different dose levels and a corresponding set of controls.[31] Several official bodies, including the US FDA, JECFA, the SCF and the UK's CoT, have discounted the findings of these studies, complaining that they did not adopt a standard protocol.

While the Ramazzini protocol was non-standard, those deviations from the standard by using more animals in more dose groups, and allowing them to die naturally, together meant that the Ramazzini provided far greater sensitivity than could be obtained from a standard study. Keeping and taking care of the animals until they died may not be common practice, but since public health policy should seek to protect consumers throughout their lives and not just until, for example, they reach retirement, suggests that the Ramazzini protocol might well provide a better model of the risk to the population of Europe than any study that 'sacrifices'

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[28] Soffritti M, Belpoggi F, Esposti DD and Lambertini L, 'Aspartame induces lymphomas and leukaemias in rats' *European Journal of Oncology*, 2005, 10,107–116; www.ramazzini.it/fondazione/docs/AspartameGEO2005.pdf; Soffritti M, Belpoggi F, Degli Esposti D, Lambertini L, Tibaldi E and Rigano A, 2'First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats' *Environmental Health Perspectives*, 2006, 114, 379-385; Soffritti M, Belpoggi F, Tibaldi E, Degli Esposti D and Lauriola M, 'Life-span exposure to low doses of aspartame beginning during pre-natal life increases cancer effects in rats', *Environmental Health Perspectives*, 2007, 115, 1293-1297

[29] M Soffritti et al, 'First experimental demonstration of the multipotenial carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats' *Environmental Health Perspectives*, 2005, Vol. 114, No. 3, March 2006 pp. 379-385 available at www.ehponline.org/docs/2006/114-3/toc.html

[30] Soffritti M, Belpoggi F, Degli Esposti D, Lambertini L, 'Aspartame induces lymphomas and leukaemias in rats', *European Journal of. Oncology*, 2005, Vol. 10, No 2, pp. 107-116

[31] See http://www.laleva.org/eng/2006/05/european_ramazzini_foundation_stands_behind_aspartame_study_results_announces_ongoing_research_on_artificial_sweeteners.html

the animals prematurely. Indeed premature sacrifice might well result in generating 'false negatives', and unacknowledged ones at that!

The abstract of the Ramazzini paper reported that the 2005 study had:

> "…demonstrated for the first time that APM is a multipotential carcinogenic agent, capable of inducing, in our experimental conditions: a) a significant, dose-related increased incidence of malignant tumor-bearing animals in males ($p \leq 0.05$) and in females ($p \leq 0.01$), in particular in females treated at 50,000 ppm ($p \leq 0.01$); b) a significant dose-related increase in lymphomas/leukaemias in both males ($p \leq 0.05$) and females ($p \leq 0.01$), in particular in females treated at doses of 100,000 ($p \leq 0.01$), 50,000 ($p \leq 0.01$), 10,000 ($p \leq 0.05$), 2,000 ($p \leq 0.05$), or 400 ppm ($p \leq 0.01$); c) a significant, dose-related increased incidence ($p \leq 0.01$), of transitional cell carcinomas of the renal pelvis and ureter and their precursors (dysplasias) in females treated at 100,000 ($p \leq 0.01$), 50,000 ($p \leq 0.01$), 10,000 ($p \leq 0.01$), 2,000 ($p \leq 0.05$), or 400 ppm ($p \leq 0.05$); d) a significant, dose-related increased incidence of malignant schwannomas of peripheral nerves ($p \leq 0.05$) in males.."

In the 2006 paper, the abstract states:

> "The results of the study show: a) a significant dose-related increase of malignant tumor-bearing animals in males ($p<0.01$), in particular in the group treated at 2000 ppm ($p<0.01$); b) a significant increase of the incidence in lymphomas/leukemias in males treated at 2000 ppm ($p<0.05$) and a significant dose-related increase of the incidence of lymphomas/leukemias in females ($p<0.01$), in particular in the group treated at 2000 ppm ($p<0.01$); c) a significant dose-related increase of the incidence of mammary cancer in females ($p<0.05$), in particular in the group treated at 2000 ppm ($p<0.05$)…The results of this carcinogenicity bioassay not only confirm, but also reinforce the first experimental demonstration of APM's multipotential carcinogenicity at a dose level close to the acceptable daily intake (ADI) for humans. Furthermore, the study demonstrates that when lifespan exposure to APM begins during fetal life, its carcinogenic effects are increased."

The comments provided by the panel's draft on the Ramazzini studies state:

> In 2006, at the request from the European Commission, the Scientific Panel on Food Additives…assessed a long-term carcinogenicity study in rats exposed to aspartame performed by European Ramazzini Foundation (ERF) (Soffritti *et al.,* 2006). On the basis of all the evidence available from the Soffritti *et al*. (2006) study, other recent studies and previous evaluations, the AFC Panel concluded that there was no reason to revise the previously established ADI for aspartame of 40 mg/kg bw/day as established by the SCF in

> 1984…The [UK] Committee on Carcinogenicity of Chemicals in Food Consumer Products and the Environment (COC) also evaluated the Soffritti *et al*. (2006) study on aspartame following the evaluation by EFSA (COC, 2006). In light of the limitations in the design of this study and the use of animals with a high infection rate, the COC considered that no valid conclusions could be drawn from this study. Therefore, the COC agreed that the Soffritti *et al*. (2006) study did not indicate a need for a review of the ADI for aspartame (COC, 2006). In 2009, following a request from the European Commission, the ANS Panel delivered a scientific opinion on the results of a second long-term carcinogenicity study in rats starting with pre-natal exposure to aspartame, performed by the ERF (Soffritti *et al.*, 2007). The ANS Panel concluded that there was no indication of any genotoxic or carcinogenic potential of aspartame and no reason to revise the previously established ADI for aspartame of 40 mg/kg bw/day (EFSA 2009a, 2009b)." (page 35, lines 871-887)

Apart from the deviations from conventional, but less sensitive, protocols the panel's main complaint about the Ramazzini study is that there was a high rate of (respiratory) infections in the rats used in the study. While that is true, it is no less true that the rates of respiratory infections amongst the groups exposed to doses of the test compound were not significantly different from the rate in the control groups, therefore the rates of infection cannot account for the dose-related increased in cancer incidence, and therefore do not provide sound grounds for discounting the findings.

Of course, there were imperfections in the studies carried out at the Ramazzini Foundation, but all studies are characterised by some imperfections. The panel refers to "…the limitations in the design of this study…" when in fact the study had been designed and implemented so as to diminish the limitations that customarily attend studies that conform to conventional protocols. Because the Ramazzini studies were more sensitive than conventional studies, they are less likely than conventional studies to have generated either false positives or false negatives, but the panel neglected to acknowledge that fact.

While it has become customary for bodies such as the SCF, JECFA and EFSA to portray studies showing no statistically significant increases in cancer rates with increasing doses as if proving safety, it would be more accurate if their interpretations were to state that, if the compound is carcinogenic, and if rodents are good models for humans, than the increase in cancer rates is unlikely to be more than eg 5%. But accurate interpretations along those lines are never provided. Instead, 'negative' results from insensitive tests are routinely portrayed as definitive.

The EFSA panel, and the previous officials judgements on which it has drawn, however highlight and exaggerate the imperfections in the Ramazzini studies, whiles under-reporting or entirely neglecting the shortcomings of other studies that

fail to suggest aspartame pose any risks. The panel discounted the Ramazzini work as a set of false positives, while accepting as true negatives, the negatives from studies that had many more and far more serious imperfections. That reveals a serious asymmetry that runs through the panel's draft.

3. In 2010, the results emerged from a second long-term rodent feeding study from the Ramazzini Foundation, but in this case the study used mice.[32] The study's abstract stated that:

> **Methods**
> Six groups of 62–122 male and female Swiss mice were treated with APM in feed at doses of 32,000, 16,000, 8,000, 2,000, or 0 ppm from prenatal life (12 days of gestation) until death. At death each animal underwent complete necropsy and all tissues and organs of all animals in the experiment were microscopically examined.
> **Results**
> APM in our experimental conditions induces in males a significant dose-related increased incidence of hepatocellular carcinomas ($P<0.01$), and a significant increase at the dose levels of 32,000 ppm ($P<0.01$) and 16,000 ppm ($P<0.05$). Moreover, the results show a significant dose-related increased incidence of alveolar/bronchiolar carcinomas in males ($P<0.05$), and a significant increase at 32,000 ppm ($P<0.05$).
> **Conclusions**
> The results of the present study confirm that APM is a carcinogenic agent in multiple sites in rodents, and that this effect is induced in two species, rats (males and females) and mice (males). No carcinogenic effects were observed in female mice."[33]

The panel says:

> "In 2011 the ANS Panel and EFSA evaluated a new long-term carcinogenicity study in mice exposed to aspartame from the 12th day of fetal life until death (Soffritti *et al.*, 2010)…The authors…concluded that aspartame induced cancer in the livers and lungs of male Swiss mice. EFSA and the ANS Panel observed that the hepatic and pulmonary tumour incidences reported by Soffritti *et al.* (2010) all fell within their own historical control ranges for spontaneous tumours and noted that Swiss mice are known to have a high background incidence of spontaneous hepatic and pulmonary tumours. The overall conclusion by the ANS Panel and EFSA was that the information available from the Soffritti *et al.* (2010) publication did not give

[32] Soffritti M, Belpoggi F, Manservigi M, Tibaldi E, Lauriola M, Falcioni L and Bua L, 'Aspartame administered in feed, beginning pre-natally through life span, induces cancers of the liver and lung in male Swiss mice', *American Journal of Industrial Medicine*, 2010, 53, 1197-1206
[33] Ibid p. 1197

> reason to reconsider the previous evaluations of aspartame (EFSA 2011a, 2011b)…EFSA concluded that there was no evidence available to support a causal relationship between the consumption of artificially sweetened soft drinks and preterm delivery and that additional studies were required to reject or confirm the association (EFSA, 2011b)."[34]

The panel's comment that the relevant cancer incidence rates in the mice: "…all fell within their own historical control ranges for spontaneous tumours and noted that Swiss mice are known to have a high background incidence of spontaneous hepatic and pulmonary tumours…" does not provide conclusive grounds for discounting the findings. When toxicological experiments are analysed and interpreted, there are always choices to be made about whether to compare test groups with the concurrent controls or with the historical averages for controls. By selecting a preferred comparator, the apparent significance of a finding might be increased or diminished.

In general, however, it is widely acknowledged that concurrent controls provides a more appropriate comparator than historical controls, precisely because they were concurrent and therefore a closer match to actual test conditions than historical averages. In this case, the panel selected historical controls while the authors emphasized concurrent controls. It is noteworthy that, when commenting on the Ramazzini Foundation's earlier rat study, the panel treated the concurrent controls as a suitable comparator. This panel, and the previous EFSA panel in 2011, selected historical controls and so explained how they came to treat these results as a false positive. But the panel's choice to compare to historical averages only amounted to invoking a hypothesis about which comparator might be more appropriate, not providing evidence to that effect. This is further evidence of the panel's asymmetric concern with potential false positives and false negatives.

4. In 2010, Halldorsson et al published the results of a large-scale long-term (7-year) epidemiological study of sweetener consumption among 59,334 women in Denmark[35], which was funded by a grant from the EU, and they reported an unexpected dose-related correlation between intakes of artificial sweeteners and the premature delivery of babies. As artificial sweeteners other than aspartame can be expected to have contributed to the results, the premature delivery of babies may not be solely attributable to aspartame, but the EFSA panel interpreted it as if it had no bearing on the risks that aspartame might pose, even though in Denmark artificially-sweetened beverages are most commonly sweetened with aspartame.

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[34] pp 35-36 lines 896-913

[35] Halldorsson TI, Strom M, Petersen SB and Olsen SF, 'Intake of artificially sweetened soft drinks 5967 and risk of preterm delivery: a prospective cohort study in 59,334 Danish pregnant women', *The American Journal of Clinical Nutrition*, 2010, 92, 626-633

The authors' abstract stated:

> "**Objective**:
> We examined the association between intakes of sugar sweetened and artificially sweetened soft drinks and preterm delivery. Design: We conducted prospective cohort analyses of 59,334 women from the Danish National Birth Cohort (1996–2002). Soft drink intake was assessed in mid pregnancy by using a food frequency questionnaire. Preterm delivery (,37 wk) was the primary outcome measure. Covariate information was assessed by telephone interviews.
> **Results**:
> There was an association between intake of artificially sweetened carbonated and noncarbonated soft drinks and an increased risk of preterm delivery (P for trend: _0.001, both variables). In comparison with women with no intake of artificially sweetened carbonated soft drinks, the adjusted odds ratio for women who consumed 1 serving of artificially sweetened carbonated soft drinks/d was 1.38 (95% CI: 1.15, 1.65). The corresponding odds ratio for women who consumed 4 servings of artificially sweetened carbonated soft drinks/d was 1.78 (95% CI: 1.19, 2.66). The association was observed for normal-weight and overweight women. A stronger increase in risk was observed for early preterm and moderately preterm delivery than with late-preterm delivery. No association was observed for sugar-sweetened carbonated soft drinks (P for trend: 0.29) or for sugar-sweetened noncarbonated soft drinks (P for trend: 0.93).
> **Conclusions**:
> Daily intake of artificially sweetened soft drinks may increase the risk of preterm delivery. Further studies are needed to reject or confirm these findings."[36]

The panel firstly comments on Halldorsson et al, on page 35-6, lines 905-917, in the following terms as:

> "The authors…concluded that there was an association between intake of artificially sweetened soft drinks and preterm delivery in the cohort; however, additional studies were required to reject or confirm the association. The ANS Panel advised EFSA on the need for epidemiological expertise to provide additional insights on the methodology and statistical aspects of this study, taking into account confounding factors (EFSA, 2011a). EFSA concluded that there was no evidence available to support a causal relationship between the consumption of artificially sweetened soft drinks and preterm delivery and that additional studies were required to reject or confirm the association (EFSA, 2011b). In 2011, the French Agency for Food, Environmental, and Occupational Health and Safety (ANSES) also concluded that no causal relationship between the consumption of

[36] Am J Clin Nutr 2010; vol 92: p626

> artificially sweetened beverages and the risk of pre-term delivery was established, and, as the authors of the Halldorsson study mentioned, there was a need to perform further studies to negate or confirm the results (ANSES, 2011)."

EFSA Panel comments again on this study, pages 86-7 lines 3064-5: "Statistically significant trends were found in the risk of pre-term delivery with increasing consumption of artificially sweetened drinks …"

The Panel then concedes: (page 87 lines 3076 -84):

> "…that the prospective design and large size of the study sample were major strengths, and there were no major flaws in the methods used. However, risk estimates may have been inflated by residual confounding (including by year of delivery). In addition, the Panel noted that it was not possible to identify a mode of action for the association between pre-term delivery and an exposure measure based on consumption of artificially sweetened drinks. Not all confounding factors are accounted for (i.e. not taking into account other dietary sources of methanol, or distinguishing the use of a specific artificial sweetener, e.g. aspartame). Therefore, given these limitations, the Panel agreed with the authors who concluded that replication of their findings in another experimental setting is warranted."

It is conspicuous that the panel acknowledged "…that the prospective design and large size of the study sample were major strengths, and there were no major flaws in the methods used…" but sought to discount the results by postulating that several possible confounding factors might have contributed to the increased risks. The panel provided no data to substantiate that hypothesis, but rather treated the possible availability of such hypotheses as sufficient reasons to discount the findings.

It is worth noting that Halldorsson et al never claimed that they had causal proof of a link between consuming eg aspartame and premature births, but rather that they had provide suggestive evidence, which should be followed up in subsequent studies. The EFSA panel however fails to call for follow-up studies; instead it portrays the issue of aspartame's safety as definitively settled.

5. In 1998, Trocho et al published a study of the biological fate of the methanol that derives from the decomposition of aspartame 1998.[37] The authors' summary of their study is reproduced below.

Summary

Adult male rats were given an oral dose of 10 mg/kg aspartame ^{14}C-labelled in the methanol carbon. At timed intervals of up to 6 hours, the radioactivity in plasma and several organs was investigated. Most of the radioactivity found (>98 % in plasma, >75 % in liver) was bound to protein. Label present in liver, plasma and kidney was in the range of 1-2 % of total radioactivity administered per g or mL, changing little with time. Other organs (brown and white adipose tissues, muscle, brain, cornea and retina) contained levels of label in the range of 1/12 to 1/10th of that of liver. In all, the rat retained, 6 hours after administration about 5 % of the label, half of it in the liver. The specific radioactivity of tissue protein, RNA and DNA was quite uniform. The protein label was concentrated in amino acids, different from methionine, and largely coincident with the result of protein exposure to labelled formaldehyde. DNA radioactivity was essentially in a single different adduct base, different from the normal bases present in DNA. The nature of the tissue label accumulated was, thus, a direct consequence of formaldehyde binding to tissue structures. The administration of labelled aspartame to a group of cirrhotic rats resulted in comparable label retention by tissue components, which suggests that liver function (or its defect) has little effect on formaldehyde formation from aspartame and binding to biological components. The chronic treatment of a series of rats with 200 mg/kg of non-labelled aspartame during 10 days resulted in the accumulation of even more label when given the radioactive bolus, suggesting that the amount of formaldehyde adducts coming from aspartame in tissue proteins and nucleic acids may be cumulative. It is concluded that aspartame consumption may constitute a hazard because of its contribution to the formation of formaldehyde adducts.

The study by Trocho and colleagues was supported in part by a Public Health Service grant from the National Cancer Institute and by the California Department of Health Services. The authors concluded that aspartame consumption may be hazardous because of its contribution to the formation of formaldehyde adducts.

In response, the EFSA panel states:

> "…the methodology used by Trocho was not able to differentiate between 14C incorporated into proteins through the metabolic one carbon tetrahydrofolate pathway and direct covalent reaction (e.g. through Schiff base formation) of formaldehyde with proteins. The authors failed to compare the single radioactive species obtained after

[37] Trocho C, Pardo R, Rafecas I, Virgili J, Remesar X, Férnandez-Lopéz JA and Alemany M, 1998. 'Formaldehyde derived from dietary aspartame binds to tissue components in vivo' *Life Sciences*, 1998, 63, 337-349

> hydrolysis of plasma protein and derivatisation of amino acids, with several of the amino acids susceptible to reaction with formaldehyde. This did not exclude the possibility that the single radioactive species in hydrolysates was not a trace level of a Maillard adduct (and therefore an artefact from sample processing) as well as omitting other controls."[38]

The panel's remark that the study did '…not exclude the possibility…' revealed that it had no evidence that the results obtained by Trocho et al were a false positive, but it chose to treat them as a false positive because that possibility could not be excluded, by reference for example to a hypothesis that was not in turn supported by evidence. The panel chose to treat the result of this study as unreliable because it was not totally conclusive; it is however conspicuous that the panel were willing to treat apparently negative studies as if conclusive, without considering corresponding hypotheses that might have discredited them. For the panel, a guess as to a possibility was sufficient to discount these positive findings . That revealed that the hurdle set for apparent positives was exceptionally high, whereas the hurdle that apparently negative studies needed to cross to be deemed reliable was far lower.

6 & 7. Abhilash et al, 2011 and 2013

In 2011 and 2013 Abhilash et al published a pair of papers in which they reported firstly effects of aspartame on the livers of rats and secondly on rats' brains.[39] The studies were conducted at the Mahatma Gandhi University, in India, and funded from independent non-commercial sources.

The abstract of the first paper read:

> "The present study evaluates the effect of long term intake of aspartame, the artificial sweetener, on liver antioxidant system and hepatocellular injury in animal model. Eighteen adult male Wistar rats, weighing 150–175 g, were randomly divided into three groups as follows: first group was given aspartame dissolved in water in a dose of 500 mg/kg b.wt.; the second group was given a dose of 1000 mg/kg b.wt.; and controls were given water freely. Rats that had received aspartame (1000 mg/kg b.wt.) in the drinking water for 180 days showed a significant increase in activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and c-glutamyl transferase (GGT). The concentration of reduced glutathione (GSH) and the activity of glutathione peroxidase (GPx), and glutathione reductase (GR) were

[38] pages 53-54: lines 1474-1505

[39] Abhilash M, Paul MV, Varghese MV and Nair RH, 'Effect of long term intake of aspartame on antioxidant defense status in liver' *Food and Chemical Toxicology*, 2011, 49, 1203-1207; Abhilash M, Sauganth Paul MV, Varghese MV and Nair RH, 'Long-term consumption of aspartame and brain antioxidant defense status' *Drug and Chemical Toxicology*, 2013, 39, 135-140

significantly reduced in the liver of rats that had received aspartame (1000 mg/kg b.wt.). Glutathione was significantly decreased in both the experimental groups. Histopathological examination revealed leukocyte infiltration in aspartame-treated rats (1000 mg/kg b.wt.). **It can be concluded from these observations that long term consumption of aspartame leads to hepatocellular injury and alterations in liver antioxidant status mainly through glutathione dependent system**." (emphasis added)

The abstract of the second paper reads:

> "The present study investigated the effect of long-term intake of aspartame, a widely used artificial sweetener, on antioxidant defense status in the rat brain. Male Wistar rats weighing 150-175 g were randomly divided into three groups as follows: The first group was given aspartame at a dose of 500 mg/kg body weight (b.w.); the second group was given aspartame at dose of 1,000 mg/kg b.w., respectively, in a total volume of 3 mL of water; and the control rats received 3 mL of distilled water. Oral intubations were done in the morning, daily for 180 days. The concentration of reduced glutathione (GSH) and the activity of glutathione reductase (GR) were significantly reduced in the brain of rats that had received the dose of 1,000 mg/kg b.w. of aspartame, whereas only a significant reduction in GSH concentration was observed in the 500-mg/kg b.w. aspartame-treated group. Histopathological examination revealed mild vascular congestion in the 1,000 mg/kg b.w. group of aspartame-treated rats. **The results of this experiment indicate that long-term consumption of aspartame leads to an imbalance in the antioxidant/pro-oxidant status in the brain, mainly through the mechanism involving the glutathione-dependent system**."[40] (emphasis added)

Not surprisingly, the panel comments (page 60 lines 1807-1817) on the small size of the samples of rats; 6 animals per group is a small sample. They also complained that only two doses were tested and the dose at which some statistically significant effects were reported was 25 times greater than the ADI. What the panel did not acknowledge however was that it accepted data from apparently negative studies with similar sized test groups, and that the practice of using high doses to compensate for a small sample size is a widely adopted and customary practice. The panel also remarked that the observed changes were mild and limited both qualitatively (as many markers of antioxidant system were unchanged) and quantitatively. The panel argues that the findings cannot be interpreted in the absence of historical values from the institute for these rats. The panel however fails to make similar demands in relation to the majority of studies that are apparently negative.

[40] See http://www.ncbi.nlm.nih.gov/pubmed/22385158 accessed 12 February 2013

The Panel also noted that the method used by the authors for the determination of GSH was not specific for GSH (since it detects a variety of thiols), and remarked that focal inflammatory infiltration of the liver is a variable (even within the same liver) but a common occurrence in rodents, particularly in the portal tract regions of the liver. In conclusion the panel states that it: "…considered that the histopathological findings presented in the reports did not convincingly support the conclusion of the authors."

Once again, it is evident that the implicit hurdle for studies indicating apparently positive evidence of harm is set very high, namely as sufficiently conclusive to provide 'convincing support', which contrasts markedly with the implicit height of the hurdle by reference to which apparently negative studies are judged. In those cases mere plausibility is often sufficient. The panel discounted the conclusions of these studies by opportunistically invoking hypotheses, not by reference to specific evidence.

8. Rencuzogullari et al 2004[41]

The paper by Rencuzogullari et al reported on their study designed to test the genotoxicity of aspartame with 3 different types of tests: 1) *in vitro* in a sister chromatid exchange assay, 2) a chromosomal aberration test and 3) a micronucleus test on human lymphocytes. The research was funded from an independent non-commercial source.

Rencuzogullari and colleagues reported that they had found dose-related and statistically significant increases for chromosomal aberrations after both 24 and 48 hours and for induction of micronuclei, although only at the highest dose-levels employed (2000 μg/ml).[42]

EFSA responded saying:

> "The Panel noted that it cannot be excluded that the positive findings resulted from indirect effects (non-physiological culture conditions) since pH and osmolality were not reported. This conclusion is supported by negative findings obtained for SCEs in parallel cultures; however, these are not usually induced by indirect effects. The possible involvement of an indirect mechanism in the reported clastogenic effect is also supported by the fact that the study was performed in the absence of S9 metabolism: in these experimental conditions, no DNA damaging activity of aspartame is expected, as the molecule does not show any electrophilic centre directly reactive

[41] Rencuzogullari E, Tuylu BA, Topaktas M, Ila HB, Kayraldiz A, Arslan M and Diler SB, 'Genotoxicity of aspartame', *Drug and Chemical Toxicology*, 2004, 27, 257-268
[42] EFSA Panel draft, pages 53-54: lines 1474-1505

with DNA. The Panel considered that the methods implemented were not sufficiently robust to support the results reported."[43]

The pattern observed here matches once again a pattern encountered previously and discussed above. An apparently positive finding of possible toxicity is discounted by reference to opportunistically-invoked hypotheses, for which no evidence is provided. The implicit hurdles by reference to which these apparently positive findings were judged by the panel are very high; they demand in effect conclusive proof. The implicit hurdled by reference to which apparently negative results are judged are far less demanding and more forgiving. This betrays a consistently asymmetric pattern and an implicit bias that characterises the panel's entire draft.

9. US National Toxicology Program, 2005[44]

The panel reports (page 63 lines 1941-1953) a set of:

> "Peripheral blood micronucleus tests…conducted in male and female transgenic mice…after 9 months of exposure to aspartame at doses ranging from 3.1 to 50 g/kg diet…In female…haploinsufficient mice, the results of the test were judged positive by the authors of the study, based on a trend test revealing a statistically significant 2.3 fold increased frequency of micronucleated erythrocytes seen in the 50 g/kg diet group… However, the Panel noted that the incidence of micronucleated erythrocytes in female controls was the lowest among the historical control values of the same laboratory; this rendered the outcome of the trend analysis positive. Nevertheless, the observed incidence of micronucleated erythrocytes in the highest dose group fell outside the range of the historical controls. However, the Panel also noted that the reported increase in micronucleated erythrocytes was observed in one gender only… (positive in female but not in male p53 haploinsufficient mice) but negative in the other two strains, and overall, did not indicate a genotoxic potential for aspartame."

Once again, opportunistic grounds are invoked to discount an apparently positive finding, even though the study came from one of the leading US government research institutions. Given that the results could be interpreted differently when compared to concurrent controls or to historical controls, the panel chooses the historical controls, even though *ceteris paribus* concurrent controls provide the most appropriate comparator. Furthermore, the fact that the adverse effect was only in the females but not the males does not entail that the apparent effects were

[43] Op cit page 62 lines 1899-1907

[44] NTP (US National Toxicology Program), 2005. NTP report on the toxicology studies of aspartame (CAS No. 22839-47-0) in genetically modified (FVB Tg.AC hemizygous) and B6.129-Cdkn2atm1Rdp (N2) deficient mice and carcinogenicity studies of aspartame in genetically modified [B6.129-Trp53tm1Brd (N5) haploinsufficient] mice (feed studies).National Toxicology Program Genetically Modified Model Report, Oct. 2005, pp. 1-222

spurious. There is no good reason why adverse effects should only be deemed real and toxicological significant if they occur in both genders. The panel does not require gender symmetry from ostensibly negative studies.

10. Bandyopadhyay et al. 2008[45]

The panel discusses Bandyopadhyay et al. 2008 on pages 63-4, lines 1963-9. That study was funded by the University Grants Commission, New Delhi. (*pers comm* email, 1 February 2013), ie by a non-commercial publicly-funded source. The panel reports that the study involved administering:

> "… aspartame as a single dose of 0 (control), 7, 14, 28 and 35 mg aspartame/kg bw to mice (four males/group) by oral gavage, and at the highest dose-level, aspartame was reported to induce DNA damage in bone marrow cells." However, the Panel evaluated the study (lines 1965-9) as poorly reported and noted that the dose levels used were low compared to other studies reporting negative results, and that an insufficient number of cells was scored (total of 50 cells/animal). Therefore, the Panel considered that the methods implemented were not sufficiently robust to support the results reported, and that no conclusion could be drawn from it."

The panel's tactic is to refer to other studies that had reported negative results, but without any explanation as to why their indications should be preferred over those reported by Bandyopadhyay et al. The implicit premise seems to be that a negative study can always trump a positive one, though never the other way round; but such a premise simply begs the question at issue.

11. AlSuhaibani (2010)[46]

The panel observes that:

> "AlSuhaibani…tested aspartame for its ability to induce chromosome aberrations (CA) SCE and to affect the mitotic index (MI) in bone marrow cells of mice (five males/group; by gavage) at dose levels of 0 (control), 3.5, 35 and 350 mg aspartame/kg bw. The authors concluded that aspartame induced CA at 35 and 350 mg/kg bw, but neither dose level induced SCE nor decreased the MI. The Panel noted that an insufficient number of cells were scored... Furthermore, no positive control was included in the study and any supplementary information on cytotoxicity relevant for CA and SCE-analysis in the present experiment was lacking. The Panel considered that the methods implemented were not sufficiently

[45] Bandyopadhyay A, Ghoshal S and Mukherjee, A, 2'Genotoxicity testing of low-calorie sweeteners: aspartame, acesulfame-K, and saccharin', *Drug and Chemical Toxicology*, 2008, 31, 447-457

[46] Alsuhaibani ES, 'In vivo cytogenetic studies on aspartame', *Comparative and functional genomics*, 2010, pii: 605921

> robust to support the results reported, and that no conclusion could be drawn from the study." [47]

While the panel complained that an insufficient number of cells had been scored, they provided no indication as to how many might be sufficient, or a reference to a source or sources for such a figure. AlSuhaibani may not have included a positive control, but studies on the genotoxicity of aspartame, and many other compounds too, that have officially been deemed acceptable have neglected to include positive controls, but as long as they suggested no adverse effects, those shortcoming passed unremarked.

12. Karikas *et al*. (1998)[48]

The panel states that Karikas and colleagues:

> "…reported a non-covalent interaction of excess aspartame, aspartic acid and phenylalanine with calf thymus DNA, inferred from the altered chromatographic profile of DNA. The Panel considered these findings, obtained in an acellular system in presence of excess aspartame, of minimal relevance for the evaluation of the genotoxic potential of aspartame."

No explanation of why the findings were deemed '…of minimal relevance…' was provided by the panel. The panel's apparent dismissal seems based on nothing more than the fact that they suggest an apparent positive; which on its own appears to have been sufficient for a routine dismissal.

13 and 14. Meier et al 1990[49] and Shephard et al 1993[50]

Meier, Shephard and Lutz's non-commercially funded study is reported to have:

> "…investigated the kinetic of formation, stability and reactivity of nitrosation products of aspartic acid, aspartame, and glycine ethyl ester. Nitrosation products were obtained *in vitro*, with incubation of 40 mM substrate and nitrite at pH 2.5 for varying times. The nitrosation products displayed an 'alkylating' activity *in vitro*…" [51]

Shephard et al were funded by the Foundation for Promotion of Cancer Research of Japan. They also addressed the possible consequences of nitrosation, and the

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[47] page 64 lines 1978-86)

[48] Karikas GA, Schulpis KH, Reclos G and Kokotos G, 'Measurement of molecular interaction of 6052 aspartame and its metabolites with DNA' *Clinical Biochemistry*, 1998, 31: 405-407.

[49] Meier I, Shephard SE and Lutz WK, 'Nitrosation of aspartic acid, aspartame, and glycine ethylester. Alkylation of 4-(p-nitrobenzyl)pyridine (NBP) in vitro and binding to DNA in the rat', *Mutation Research*, 1990, 238:193-201

[50] Shephard SE, Wakabayashi K and Nagao M, 'Mutagenic activity of peptides and the artificial 6365 sweetener aspartame after nitrosation' *Food and Chemical Toxicology*, 1993, 31, 323-329

[51] Page 64 lines 1993-9

panel combines its discussion of these two studies. The panel reports that in this study:

> "Aspartame and several naturally occurring dipeptides were nitrosated *in vitro* at low pH (3.5) in the presence of 40 mM nitrite and tested for mutagenicity in *Salmonella typhimurium* TA100. The nitrosation products of some dipeptides (Trp-Trp, Trp-Gly) and aspartame exhibited a direct mutagenic activity, which was related by the study authors to the nitrosation of their primary amino groups."[52]

The panel responds with:

> "…the Panel noted the harsh conditions utillised for the *in vitro* nitrosation of substrates and considered the results of doubtful relevance for the assessment of the genotoxic risk posed by the dietary intake of aspartame or other natural amino acids and dipeptides."[53]

The conditions in which the ingredients had been nitrosated were on the harsh side, but such conditions have been used in other studies, which have officially been deemed reliable, at least when they provided apparently negative results.

15. Collison *et al.* (2012a)[54]

Collison et al were funded by an independent non-commercial funder. They studied some interactive effects of neonatal exposure to monosodium glutamate and aspartame on glucose homeostasis. The panel reported that:

> "Mouse offspring (12 to 18/sex/group) were bred, weaned and maintained on the following diet groups for 17 weeks: standard diet (control), standard diet with MSG (120 mg/kg bw/day) alone, standard diet with aspartame (approximately 50 mg/kg bw/day) alone, standard diet with MSG and aspartame…Aspartame alone caused a 1.6-fold increase in fasting blood glucose and reduced insulin sensitivity…The combination of MSG and aspartame increased body weight, and caused a further 2.3-fold increase in fasting blood glucose compared to control diets… A positive correlation between aspartame intake and body weight at 6 weeks and 17 weeks…The authors concluded that aspartame exposure might promote hyperglycaemia and insulin intolerance, and MSG might interact with aspartame to impair further glucose homeostasis."[55]

[52] Page 64 lines 2000-4
[53] Page 64 lines 2005-8
[54] Collison KS, Makhoul NJ, Zaidi MZ, Al-Rabiah R, Inglis A, Andres BL, Ubungen R, Shoukri M and Al-Mohanna FA, 'Interactive effects of neonatal exposure to monosodium glutamate and aspartame on glucose homeostasis', *Nutrition and Metabolism*, 2012, 14, 9, 58
[55] Page 81 lines 2796 -2810

The panel commented that:

> "…the mouse strain used in this study is known to harbour a dominant trait showing a high susceptibility to diet-induced type-2 diabetes, as well as obesity and atherosclerosis …The Panel also noted that no dose-response was assessed in this study and that other authors (Berglund *et al*., 200826) have reported higher insulin and glucose basal levels in the C57BL/6J mice strain suggesting that those parameters vary in that mice strain. The Panel also noted that phenylalanine and glutamate can also arise from the protein content of the diet and thus the actual contribution of aspartame to the total phenylalanine and glutamate amino acids pool should be clearly defined to be able to attribute exclusively an increment in fetal amino acid pool to aspartame intake. Finally, the Panel also observed that short term preliminary interventional trials undertaken in human volunteers suggest that test meals containing aspartame significantly reduce postprandial glucose levels and insulin levels compared to a test meal containing sucrose (Anton *et al*., 2010)."[56]

The mouse strain might be sensitive in the way the panel complained, but toxicological principles ostensibly stipulate that judgements should be based on effects in the most sensitive variety of the most sensitive species. Unfortunately that 'principle' is more frequently breached than observed. The panel chooses to disparage the strain of mice used by Collinson and colleagues as rather variable, but the human population that the experiment was trying to model is highly variable. Moreover the panel provides no evidence that other stains are less variable. The observed effects may not have shown a linear dose-effect relationship, but there are many good biochemical reasons for recognising that not all mechanisms causing adverse changes exhibit linear dose-effect relationships. In the case of the Anton et al 2010 study, they only worked with 19 healthy lean and 12 obese individuals, which can hardly be deemed to have constituted an adequately representative sample of humanity, let alone of residents of the EU.

[56] Lines 2815-2825)

17. Collinson et al PLoS (2012b)[57]

In this non-commercially-funded study Collinson et al state that they:

> "… investigated the effects of chronic lifetime exposure to aspartame, commencing in utero, on changes in blood glucose parameters, spatial learning and memory in C57BL/6J mice."[58]

The panel's characterisation of the study is that:

> "…the effects of neonatal exposure to aspartame, commencing in utero, on changes in blood glucose parameters, spatial learning and memory in…mice…between 12 and 18 per group…administered standard diet (control) or standard diet with aspartame (approximately 50 mg/kg bw/day) for 17 weeks. Increased weight gain, increased fasting glucose levels and decreased insulin sensitivity was observed in treated male mice compared to controls. These effects were less apparent in females, which did however show significantly raised fasting glucose levels…. Overall, the authors of the study concluded that lifetime exposure to aspartame, commencing in utero, might affect spatial cognition and glucose homeostasis in C57BL/6J mice, particularly in males."[59]

To which panel responded with:

> "…only one dose was used rendering thus any assessment of dose-response relationship not possible. The Panel noted that the findings in mice reported …might not apply to other species, since in a large study on Sprague-Dawley rats (Holder, 1989) performances …was similar for rat pups given aspartame…compared to controls."

Using a single dose and a control cannot provide a characterisation of a dose-response relationship, but that does not mean that the response was one that should be discounted or neglected. The responses of Sprague-Dawley rats may well be different from those of C57BL/6J mice, but that provides no grounds for supposing that the Sprague-Dawley rats provide better models for the effects on humans than C57BL/6J mice; maybe the rat study could be criticised for failing to show effects that Collision et al found in mice. Once again implicit assumptions are a stronger influence of the panel's judgement than the data it purports to interpret.

[57] Collison KS, Makhoul NJ, Zaidi MZ, Saleh SM, Andres B, Inglis A, Al-Rabiah R and Al-Mohanna FA, 2012b 'Gender dimorphism in aspartame-induced impairment of spatial cognition and insulin sensitivity', *Public Library of Science One*, 7, e31570

[58] *Ibid.* page 1

[59] Page 81-2, lines 2826-285

18. Puică 2008 & 2009[60]

This non-commercially funded group of researchers concluded their 2008 paper by saying:

> "The chronic administration of Aspartame at prepubertal stage on juvenile rabbits induced neurodegenerative effects especially in the circumventricular organs (CVO) of hypothalamus; and severe structural and functional alterations in hypothalamic-pituitary axis. The experimental results show that there is an increased sensibility of the immature brain in prepubertal stage of onthogenetic development following chronic exposure to Aspartame. The degenerative aspects of brain and pituitary observed in Aspartame-treated rabbits; suggests that it is reasonable to assume that the same infant-to-adult relationship would be true for the Aspartame consumption in humans to children in the prepubertal period of development."

The panel responded saying:

> "…that the interpretation of these studies was not possible because of the lack of experimental details, the absence of appropriate control animals and of statistical analysis of the data." [61]

The lack of details may well be problematic, but then it is puzzling why the panel did not take the opportunity officially to request that information? If the panel had been more inquisitive it might have seen something it was not expecting.

19. Alleva *et al*, 2011[62]

Alleva and colleagues are non-commercially funded public sector research scientists in Italy. Their study examined whether exposure to aspartame might adversely influence the formation of new blood vesseesl. Their abstract says:

> "We evaluated the angiogenic effect of APM [aspartame] in an in vitro model using blood vessel development assay… Exposure to …APM increases the levels of inflammatory mediator…and their soluble receptors released from endothelial cells into the medium. APM treatment induces VEGF-pathway activation …APM at low doses is an angiogenic agent that induces regenerative cytokine production

[60] Puică C, Crăcium C, Rusu M, Cristescu M, Borsa M and Roman I, 'Ultrastructural aspects concerning the hyp*othalamus-pituitary complex reactivity following chronic administration of aspartame in juvenile rabbits. Bulletin UASVM, Veterinary Medicine*, 2008, 65, 424-429; Puică C, Crăcium C, Rusu M, Cristescu M, Borsa M and Roman I, 'Ultrastructural aspects concerning the hypothalamus-pituitary complex reactivity following chronic administration of aspartame in juvenile rats'. *Studia Universitatis "Vasile Goldiş", Seria Ştiintele Vieţii*, 2009, 19, 19-24

[61] Page 84 lines 2946-7

[62] Alleva R, Borghi B, Santarelli L, Strafella E, Carbonari D, Bracci M and Tomasetti, M, 'In vitro effect of aspartame in angiogenesis induction' *Toxicology in vitro*, 2011, 25, 286-293

leading to the activation of MAPKs and resulting in the formation of new blood vessels."[63]

The panel responded noting:

> "…that production of ROS [reactive oxygen species] could not be attributed to specific cell types but rather a general phenomenon…the authors did not evaluate the fate of aspartame in culture medium ascertaining whether it was hydrolysed to its usual metabolites or remained intact. For induction of angiogenesis, no positive and negative controls were reported. The Panel also noted that no formation of ROS in different *in vivo* and *in vitro* genotoxicity studies following treatment with aspartame or methanol (McCallum *et al*., 2011a,b) has been observed. This suggests that the finding reported might be ascribed specifically to the conditions of the study. For these reasons, the Panel considered these data not relevant for the risk assessment of aspartame."[64]

The panel's comment is puzzling because it misleadingly suggests that McCallum et al had studied effects of aspartame, but their paper only reported a test conducted with methanol, not with aspartame. The panel also failed to comment on the significant fact that the study by McCallum and colleagues was funded in part by a trade association representing methanol producers. (See Methanol Institute at http://www.methanol.org/) Once again, the panel was keen to benchmark a positive study against a negative study, rather than the other way round; the negative study is assumed to be correct, but that is an assumption not an empirical result.

20. Linda Englund-Ögge, et al[65]

Linda Englund-Ögge and her Norwegian colleagues published in 2012 the findings of their non-commercially-funded study of the impact of consuming both sugar-sweetened (SS) and artificially-sweetened (AS) soft drinks of the likelihood that pregnant women would deliver their babies prematurely. The abstract of paper says: "This study suggests that a high intake of both AS and SS beverages is associated with an increased risk or preterm delivery."[66] This epidemiological study was particularly powerful, because the researchers analysed data from a remarkably large sample comprising 60,761 women.

The panel's discussion of this study is located immediately after a discussion of Halldorsson et al, which is reviewed above as item 4. The panel prefaces its remarks on this study by saying:

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[63] op cit p 286

[64] Page 85 lines 2999-3007

[65] Englund-Ögge L, Brantsæter AL, Haugen M, Sengpiel V, Khatibi A, Myhre R, Myking S, Meltzer HM, Kacerovsky M, Nilsen RM and Jacobsson B, 'Association between intake of artificially sweetened and sugar-sweetened beverages and preterm delivery: a large prospective cohort study', *The American Journal of Clinical Nutrition*, 2012, 96, 552-559

[66] Op cit p 552

> "To explore whether the findings of Halldorsson *et al.* (2010) could be replicated, another study (Englund-Ögge *et al*., 2012) investigated the relation between consumption of artificially sweetened and sugar-sweetened soft drinks during the first 4-5 months of pregnancy and subsequent pre-term delivery in a large cohort of Norwegian women."[67]

The implication of the panel's comment is that the latter study was framed by reference to its predecessor, but that is implausible because the latter began before the former had been reported.

The panel commented on Englund-Ögge et al saying:

> "No significant trends were found in the risk of pre-term delivery with increasing consumption either of artificially sweetened drinks or of sugar-sweetened drinks. Small elevations of risk were observed with higher consumption of artificially sweetened soft drinks, but after adjustment for covariates, these reached statistical significance only when categories of consumption were aggregated to four levels, and then the odds ratio for the highest category …was only 1.11 (95% CI 1.00-1.24) in comparison with never consumption.… Associations with sugar-sweetened soft drinks tended to be somewhat stronger, with an adjusted odds ratio of 1.25 (95% CI 1.08-1.45) for consumption of at least one serving per day."[68]

EFSA Panel concludes its comments on both Halldorsson et al and Englund-Ögge, et al:

> "In summary, both studies appear to have been well designed and conducted. Noting this, the Panel concluded that even at high level of exposure to artificially sweetened soft drinks the risk of pre-term delivery is likely to be small, if any. This observation could be a consequence of uncontrolled residual confounding, and the inconsistencies in the patterns of association reinforce this uncertainty. When findings from the two studies are considered together, they do not point to a hazard concerning the intake of artificially sweetened soft drinks."[69]

Those comments are puzzling. In point of fact the findings of the Englund-Ögge, et al study do support those of Hallsorsson et al. The panel may deem the magnitude of an effect to be 'small', but without indicating how many babies would need to be delivered prematurely before the panel might acknowledging a risk or even a hazard. When remarking that the observed increased risk: "…could be a consequence of uncontrolled residual confounding…" the panel invoked an opportunistic hypothesis, but without

[67] Page 87 lines 3085-8
[68] Pages 87-8, lines 3110-8
[69] Page 88, lines 3126-31

providing any supporting evidence. They might have been diminished by 'residual confounding, but then they might not. A mention of the possibility does not justify assuming a probability. The fact that these studies compared sugar-sweetened drinks with artificially sweetened drinks, rather than aspartame-sweetened drinks, complicates their interpretation, but aspartame dominates the artificially sweetened soft drink market, so it does not put aspartame in the clear.

21. Schernhammer *et al*., 2012[70]

The panel explains that in their publicly-funded research Schernhammer and colleagues studied:

> "The risk of lymphatic and haematopoietic cancers in relation to consumption of diet soda and aspartame sweeteners added at the table was examined in two US cohorts – one of 77,218 female registered nurses and one of 47,810 male health professionals – followed prospectively from 1984 and 1986 to 2006…During follow-up, 1,324 subjects developed non-Hodgkin lymphoma (NHL), 285 multiple myeloma, and 339 leukaemia…After adjustment for potential confounders, the category of highest aspartame intake…was associated with a significantly elevated relative risk of NHL (1.64, 95%CI 1.17-2.29) and of multiple myeloma (3.36, 95%CI 1.38-8.19) in men. However, there was no consistent trend in risk with increasing exposure, and there were no corresponding elevations in risk in women."[71]

The Panel acknowledged that:

> "Major strengths of this study are its prospective design, the substantial number of cancer cases, the repeated assessment of dietary intake and the fact that various potential confounders were addressed. However, the positive findings can be given little weight, given their limitation to men, the small relative risks observed, and the lack of clear dose-response relationships."[72]

Once again the comments disparage positive findings. Why might an increased cancer risk to men not count unless it is also matched by one to women? Cancers are not always gender-blind. How large would the extra risk need to be before the panel took it seriously? The panel never says. Some might ask, why might one extra case of cancer not be one too many?

[70] Schernhammer ES, Bertrand KA, Birmann BM, Sampson L, Willett WW and Feskanich D, 'Consumption of artificial sweetener- and sugar-containing soda and risk of lymphoma and leukemia in men and women', *American Journal of Clinical Nutrition*, 2-12, 96, 1419-1428.
[71] Panel draft, page 89-90 lines 3202-3218
[72] Page 90 lines 3222-3225

Perhaps the panel is making unacknowledged assumptions about the putative benefits of consuming artificial sweeteners, but such assumptions would also deserve to be critically scrutinised. As the consumption of artificial sweeteners has grown, especially since aspartame was first marketed in the early 1980s, there has been no corresponding decline in sugar consumption; in practice and in aggregate artificial sweeteners do not substitute for sugar consumption, they supplement it. There is moreover no convincing evidence that they help people lose weight, and even some evidence suggestion that they may be appetite stimulants. So the two questions at the end of the previous paragraph deserve to be answered explicitly.

22. E23 1972[73]

One of the many early studies conducted by, or for, G D Searle (referred to by Searle, NutraSweet, Ajinomoto and the Panel as E23) examined how normal adults tolerated aspartame, in the short-term.[74] According to the panel:

> "In preliminary studies…31 men and 38 non-pregnant women (age 21-45 years) were administered aspartame under double blind conditions in capsules containing placebo, 200 mg aspartame or 300 mg aspartame. The subjects took an appropriate number of capsules per day to deliver increasing doses of aspartame"

To which EFSA says:

> "The only 'adverse' symptoms reported were mild and often contradictory (loose stools/constipation, increased/decreased appetite and headache)."[75]

The panel provides no explanation of why it surrounds 'adverse' with inverted commas. In what sense are headaches, constipation, laxation or appetite changes not adverse? The casual manner in which the panel discounts such effects is important because neurological effects, such as headaches, are amongst the acute adverse effects that have subsequently most often been reported as attributable to aspartame consumption. Moreover similar symptoms appeared in E60[76], although once again they were discounted by GD Searle and are by the panel.

Evidence that aspartame can cause headaches has been provided by double-blind crossover trails.[77] While the panel briefly discusses the study by Van den Eeden et

[73] Short Term Tolerance Of Aspartame By Normal Adults, 1972, listed by panel page 142
[74] Page 90-1 lines 3243-3256
[75] Page 93 lines 3255-6
[76] Page 91 lines 3269-81
[77] S. K. Van Den Eeden et al 'Aspartame ingestion and headaches: A randomized crossover trial', *Neurology*, October 1994, Vol. 44 no. 10 1787

al.[78] the findings are discounted because: "The Panel consider that with such a low number of participants it was not possible to draw a conclusion."[79]

But the number of subjects enrolled by Van den Eeden and colleagues was deemed too small, even though it was a similar order of magnitude to those enrolled for E23. (Further comments on the panel's treatment of Van den Eeden are given below under item number 25; see also item 24, ie Koehler and Glaros 1988 below) The panel evidently assumes that small numbers can suffice if studies provide negative indications but not if they are positive. In other words, this example provides further evidence of the panel adopting asymmetric criteria of interpretation, bias in favour of the compound.

23. Camfield et al, 1992[80]

Camfield and colleagues conducted a non-commercially funded double-blind study that involved challenging recently diagnosed epileptic children with aspartame; they reported that aspartame exacerbates symptoms in children with 'generalized absence epilepsy': The panel reported that:

> "A double-blind study was undertaken in children recently diagnosed with generalised absence seizures or also called petit mal seizures to ascertain whether aspartame would exacerbate the occurrence of such seizures…After…breakfast…children (n = 10) drank orange juice sweetened with either aspartame (40 mg/kg bw) or sucrose (1 g sucrose for every 25 mg aspartame) to achieve similar sweetness. For six hours following consumption of the juice the number and length of spike-wave bursts, indicative of an absence seizure, were determined…Each child was tested once with each substance, on two consecutive days, treatments were assigned in a random fashion. No information was provided regarding whether lunch or snacks were given. There were no significant differences in either the frequency or duration of spike-wave bursts; however, when the two factors were combined, the total time spent in spike-wave per hour of observation was significantly higher in children after consumption of aspartame compared with sucrose…"[81]

EFSA Panel remarked that the:

> "…combination of the two factors into a single measure was not adequately explained, [But not unreasonable as both matter] and

[78] Page 97 lines 3555-67
[79] Page 97 lines 3555-67
[80] Camfield, P R et al, 'Aspartame exacerbates EEG spike-wave discharge in children with generalized absence epilepsy: A double-blind controlled study', *Neurology 42*, May 1992, p 1000-3
[81] Sec 3.2.7.5. pages 95-6 lines 3493-3505

lack of control of food and drink intake before and after dosing may have affected the results."[82]

Camfield and colleagues might have provided more information about the provision of lunch and/or snacks, but then the panel could have asked them for it. It is in any case very unlikely that they would not have provided the children with food, or that the food contained much in the way of either sugar or aspartame. The journal in which the paper was published is peer-reviewed and it would be odd if those matters had not been considered, even if there might not have been space for those details in the published paper. The panel was also puzzled by the choice of indicator, although that too might have been the subject of a request for more data. It is striking however that when experimental indicators fail to suggest adverse effects from aspartame consumption, the panel never questions their suitability or relevance. The panel neglects to acknowledge that effects arising in double-blind challenge studies deserve to be taken particularly seriously, especially as the panel accept apparently negative studies that were not double-blind.

24. Koehler and Glaros (1988)[83]

Koehler and colleagues also provided a interesting non-commercially-funded double-blind crossover study on the effect of aspartame consumption amongst a sample of migraine sufferers. The panel reports that:

"…volunteers who suffered with migraines and stayed in their normal environments during a double-blind crossover study with three phases: a 4-week baseline phase and two four-week experimental phases, with a 1-week washout phase between treatments. Participants (two males, eight females; ages 18 to 47 years) consumed capsules of aspartame (300 mg) or placebo (microcrystalline cellulose) and self-recorded incidence of headaches and dietary information. The incidence of headaches did not differ from baseline during the placebo phase. Five of the eleven participants reported a higher number of migraines during the aspartame phase compared to during the baseline or placebo phases. The mean number of headaches reported was 1.72, 1.55, and 3.55 during the baseline, placebo, and aspartame phases, respectively."[84]

In other words, even in a small sample, there was a conspicuous increase in headaches in over half of the sample following aspartame ingestion, even though the subjects did not know what and when they were ingesting. The panel endeavours to discount the findings by remarking that: "No

[82] Page 96 lines 3505-7
[83] Koehler SM, Glaros A, 'The Effect of Aspartame on Migraine Headache', *Headache*, 1988, Vol 28 pp 10-13
[84] Page 96 lines 3536-4

differences were reported in the intensity or duration of migraine headaches."[85]As if that was a decisive or even relevant consideration.

The panel cites a high dropout rate, from 25 to 11 participants, as making interpretation of the results difficult, but if small sample numbers can be sufficient for negative results to be endorsed it is not clear why they need be higher before positive findings deserve not to be discounted. One explanation for the dropout rate might well be because the participants judged that the headaches that they experienced were so unpleasant that they were unwilling to remain in the study and endure the suffering. The panel neglected however to discuss such a possibility.

25. Van der Eeden et al[86]

Van Den Eeden and colleagues conducted a randomised crossover trial of the effect of aspartame consumption on headache sufferers. The panel states:

> "…a double-blind randomised crossover trial with 32 subjects self-diagnosed as sensitive to aspartame. Only 18 participants completed the full protocol, as other subjects withdrew for various reasons including adverse effects. Subjects took capsules containing either aspartame or placebo (microcrystalline cellulose) three times a day to achieve a dose of 30 mg/kg bw/day for seven days. A significantly higher (p = 0.04) occurrence of self-reported headaches was recorded following exposure to aspartame (33% of days) compared to placebo (24% of days)."[87]

The panel responded with:

> "The subjects who had excess headaches following aspartame dosing were those who had, at the beginning of the study, indicated they were 'very sure' that they were susceptible to aspartame-induced headaches. In contrast, those subjects who classified themselves as 'somewhat or not sure' reported similar headache incidence during aspartame and placebo exposure periods. The authors conclude that these results indicated that a small subset of the population was susceptible to aspartame-induced headaches…The Panel consider that with such a low number of participants it was not possible to draw a conclusion."[88]

Once again, low numbers are invoked not as grounds for a hypothesis that there may well be a problem, or as a prompt to request further studies, but as grounds for dismissing the data as if a 'false positive'. Nor does the panel explain why low

[85] Page 96 Lines 3545-7
[86] Van Den Eeden SK, Koepsell TD, Langstreth WT Jr, et al., 'Aspartame Ingestion and Headaches: A randomized Crossover Trial'. *Neurology*, 1994; 44(10):1787-93
[87] Page 97 lines 3555-67
[88] Page 97 lines 3560-67

numbers do not count against apparently negative studies that used similarly small numbers. The panel notes (line 3568) in relation to the set of studies concerning headaches that there is: "…no convincing evidence of effects of aspartame on headache." But the panel fails to provide any indication as to what it would take to convince them. Perhaps nothing short of 'knock-down causal proof' would be sufficient, as evidence from several double-blind studies is apparently insufficient. Maybe the panel would only be persuaded if headaches always and only occurred immediately after aspartame consumption? It is in any case clear that the barrier that apparently positive evidence would need to cross is exceptionally high, and far higher than that deemed essential for apparently negative findings.

26 and 27: Jacob and Stechschulte, 2008[89], **Hill and Belsito 2003**[90]

The panel referred to these two studies and reported:

> "…some case reports have been published in which associations are made between aspartame intakes, in particular the subsequent exposure to the aspartame metabolite formaldehyde, and Type IV Delayed Type Hypersensitivity (DTH) reactions in patients with proven contact sensitization to formaldehyde."[91]

EFSA responded (lines 3609-12) with:

> "However, it is not possible to establish the associations observed in these two case studies with only a limited number of patients, larger case studies are needed with double-blind placebo-controlled challenges using aspartame and placebo exposures, and should include well-defined control patient groups."

Curiously enough, however, the panel neglects to request those larger studies, nor does it suspend judgement pending the receipt of the results of such studies, it simply interprets the absence of proof as if it constituted proof of absence. That may be an all-too-familiar tactic, but it is hardly sound science.

Summary

This section has discussed 27 examples of where the EFSA panel has discounted apparently positive findings of adverse effects of aspartame. In every case they have been discounted as, in effect, falling short of providing conclusive proof. On the other hand, in every one of the 27 cases, the grounds provided by the panel were also inconclusive, frequently arbitrary and occasionally spurious; in general they are simply flimsy. The panel did not accept any positive finding as a true positive, every single one was characterised as probably or definitely a false positive. The fact is that all those 27 studies providing evidence positively

[89] Jacob SE and Stechschulte S, 'Formaldehyde, aspartame, and migraines: a possible connection', *Dermatitis*, 2008, 19, E10-11

[90] Hill AM and Belsito DV, 'Systemic contact dermatitis of the eyelids caused by formaldehyde derived from aspartame?' *Contact Dermatitis*, 2003, 49, 258-259

[91] Page 98 lines 3606-12

indicating adverse effects were funded by non-commercial sources; it is distinctly unscientific to suppose that commercially funded studies are intrinsically more reliable than independent studies.

It would be misleading to suggest that all non-commercially funded on the safety of aspartame have yielded apparently positive evidence of adverse effects. It is therefore worth noting that two examples of apparently negative non-commercially funded studies are provided by:

1. Gallus S, Scotti L, Negri E, Talamini R, Franceschi S, Montella M, Giacosa A, Dal Maso L and La Vecchia C, 2006. 'Artificial sweeteners and cancer risk in a network of case-control studies' *Annals of Oncology*, 18, 40-44; and

2. Lim U, Subar AF, Mouw T, Hartge P, Morton LM, Stolzenberg-Solomon R, Campbell, D, Hollenbeck AR and Schatzkin A, 2006. 'Consumption of aspartame-containing beverages and incidence of hematopoietic and brain malignancies' *Cancer Epidemiology, Biomarkers and Prevention*, 15, 1654-1659.

Responding to apparently 'negative' studies

This briefer section examines several of the occasions on which the panel rejected apparently 'negative' studies, and does so in the sequence in which they are discussed in the panel's draft. As suggested above, the dominant interpretative pattern revealed by the panel's draft includes an implicit rule to take apparently 'negative' studies at face value, rather than subjecting them to penetrating criticisms. There are, nonetheless a few exceptions, which deserve to be discussed here, where the studies were so poor that it was evident that no reliance could be placed on them.

A list of 8 examples where the panel discounts possible negatives as unreliable include the following items:

Study ID	Year reported	Location of panel comments
G D Searle's E81	1974	Page 61 lines 1829-1837
G D Searle's E12	1970	Page 61 lines 1855-1861
G D Searle's E44	1972	Page 61 lines 1862-1870
Rencuzogullari et al	2004	Page 62, lines 1880-4
Bandyopadhyay et al	2008	Page 62 lines1885-90
Durnev et al	1995	Pages 62-3 Lines 1909-22
Mukhopadhyay et al	2000	Page 63, lines 1923-8
Cabaniols et al	2011	Page 89, lines 3195-3201

While on those 8 occasions, the panel commented adversely on apparently negative studies, there were also other 8 occasions when the panel failed to criticise the shortcomings of apparently negative studies, apart from those the 15 studies that were deemed pivotal and flawed by the FDA in the early 1970s.

One example is provided in the discussion of one of G D Searle's very earliest studies, identified as E3, 1972:

> "In a sub-acute study, aspartame was given in the diet for 4 weeks to male and female Charles River CD rats (E3, 1972). Seven-week-old rats (*5 animals per dose group*) were administered aspartame incorporated in the diet on a w/w basis, resulting in an exposure of 0, 2000, 4000 or 10000 mg/kg bw/day. Actual consumption was estimated to be within 10% of the proposed dose. *No consistent statistically significant effect in body weight was observed, though a significant decrease in feed consumption was reported in the high-dose females at weeks 2 and 3*; however, this was not reflected in body weight gain, which increased during the treatment-period. *No adverse clinical conditions were reported during the study period and 100% survival was reported in both control and treated groups.*

> *Only five control animals (3 males and 2 females) and the animals from the high-dose groups were examined histopathologically.* No treatment-related changes were reported except that the intestinal mucosa from the treated rats was heavily coated with a clear, moderately viscous fluid."[92] (emphasis added)

Given that the number of animals per dose group was just 5, the remark that there were 'no consistent statistically significant effects' is unpersuasive. Given the normal criterion for statistical significance, namely less than 1 chance in 20 of the change having been a random occurrence, 4 out of the 5 rats could have been adversely effected, and that pattern would still fall short of 'statistical significance'.

This study, given its small size, when interpreted in terms of statistical significance was bound to be irremediably insensitive. Moreover, as "…only…3 males and 2 females…from the high-dose groups were examined histopathologically…" the resulting histopathological data should have been discounted as uninformative. In this case however, an apparent negative was reported by the panel as if a reliably true negative when at best the study was conspicuously un-illuminating and quite possibly provided a false negative. This is an example of where the panel accepted a homeopathic dose of apparently negative data as if unproblematically reliable, while (as explained in the previous section) discounting a substantial weight of apparently positive evidence.

The evidence provided by the dossier of documents I delivered to EFSA in the autumn of 2011 shows that none of the studies submitted for review by the US FDA Bureau of Foods Task Force, namely: E-5, E-77/78, E-89 and those that were submitted for review by the UAREP, namely: E-9, E-11, E-19, E-28, E-33/34, E-70, E-75/76, E-86/87, E-88 and E-90 should be treated as if they were reliable. While the conclusions of the Bureau of Foods Task Force and of the UAREP perversely portrayed the shortcomings of those studies as providing insufficient grounds for discounting them, both of those exercises have subsequently been irredeemably repudiated by key protagonists who were involved in those exercises.

In particular statements by Dr Jacqueline Verrett, which are on the record and published, including her testimony to the US Senate Committee on Labor and Human Resources, 3 November 1987, show that the terms of reference imposed on the Bureau of Foods Task Force were inappropriately narrow, and framed to prevent the taskforce from addressing the most critical failings of the studies.

Similarly, a critique of the UAREP Report provided by Dr Adrian Gross, a former FDA pathologist, in his letters to Senator Metzenbaum, which were included in the record of the US Senate Committee on Labor and Human Resources, 3 November

[92] Page 59 lines 1742-52

1987.[93] Gross explained that the terms of reference adopted for the UAREP review, and chosen by G D Searle and a senior FDA official (who subsequently took a leading role in a soft drinks industry trade association) were also inappropriately narrow, and framed to prevent UAREP pathologists from addressing the most critical failings of the studies, from which pathology samples were reviewed. As Gross repeatedly explained, the UAREP panel failed to examine critically the practices that had resulted in those samples being mounted on the pathology slides.

A few conspicuous examples of the panel reviewing the problematic early Searle studies and interpreting them uncritically, while failing to address their shortcoming are provided by the discussion of:

Study ID	**Year reported**	**Location of panel comments**
G D Searle's E75	1974	Page 65 lines 2030 – 2062
G D Searle's E33/34	1974	Page 66 lines 2063-2105
G D Searle's E70	1974	Page 66-7 lines 2106-2161 and on page 68 lines 2175-83

It is noteworthy that in relation to E70 the panel comments:

> "…Some statistically significant changes in relative organ weights were reported but these were not accompanied by histopathological alterations and these were therefore considered by the authors to be of no biological significance."[94]

While the authors of the study may have preferred to treat those statistically significant changes as toxicologically insignificant, it is less clear why the panel chose uncritically adopted that interpretation.

Another set of examples of where the panel fails to criticise the shortcoming of putative false negatives comes in Section 3.2.5.2.2 on developmental studies.[95] At three points in that brief section the panel refers to 'negative geotaxis' in studies as if it was relevant and as if its absence provided some reassurance.[96] The panel failed however to refer to work such as that by B A Motz & J R Alberts, 'The validity and utility of geotaxis in young rodents', in *Neurotoxicology and Teratology*, 2005, Vol 27, pp 529 – 533, who argued that in infant rodents 'negative geotaxis' is a spurious indicator with no reliable validity.

When discussing Holder (1989), the panel reports[97] that the study used only 10 rats per group, but then treated the resultant data as sufficient to confirm the

[93] Available as http://www.dorway.com/gross.txt
[94] Page 67 lines 2121-3
[95] pages 80-81 lines 2750-2787
[96] See Mahalik and Gautieri (1984) & McAnulty *et al*. (1989) & Holder (1989)
[97] Pages 80-81 lines 2772-2787

absence of the endpoints that had been monitored. The panel would have displayed greater scientific rigour if it had drawn attention to the lack of sensitivity of a test using such small groups. A putative false negative was yet again exempted from even the most rudimentary criticism.

When discussing Searle's 1972 study known as E23, the panel remarks:

> "In preliminary studies...31 men and 38 non-pregnant women (age 21-45 years) were administered aspartame under double blind conditions in capsules containing placebo, 200 mg aspartame or 300 mg aspartame. The subjects took an appropriate number of capsules per day to deliver increasing doses of aspartame"[98]

The panel then reports that: "The only 'adverse' symptoms reported were mild and often contradictory (loose stools/constipation, increased/decreased appetite and headache)."[99] The panel fails to explain why it surrounded the word adverse with inverted commas; why might those effects not be deemed adverse? This issue is important because once aspartame entered the food supply those symptoms and adverse effects are precisely the ones that have most frequently been reported by consumers. Moreover the same symptoms are reported in respect of E23[100] and E60[101], but yet again the evidence of those adverse effects was discounted G D Searle in and since the 1970s, and in this draft by the EFSA panel.

The panel represented G D Searle's 1972 study known as E 43, as providing evidence that:

> "…aspartame was not mutagenic. The Panel considered that the methods implemented were sufficiently robust to support the results reported, but considered the study limited since mitotic indexes were not reported"[102]

This is a example of when an apparent negative from small study is treated not just as negative, but as showing that aspartame is not mutagenic –without qualification. That must be contrasted with the occasions, discussed above, when apparently positive evidence of adverse effects in small studies was discounted because of the small sample size.

[98] Pages 90-1 lines 3243-3256
[99] Page 91 lines 3255-6
[100] Page 91 lines 3257-68
[101] Page 91 lines 3269-81
[102] Page 61 lines 1847-1854

Summary of implicit and unacknowledged criteria of interpretation for bopth 'positive' and 'negative studies

The detailed discussions above demonstrate that the panel implicitly adopted a skewed and biased set of interpretative criteria. The criteria of interpretation of apparently positive studies were deployed in ways that allowed the panel to dismiss every single one of them, as if false positives. In relation to apparently negative studies the panel deemed at least 80 of them to be unproblematically reliable, ie as true negatives. And while it did discount several apparently negative studies as unreliable, it did so only on a handful of occasions. Moreover, even when discussing evidently inadequate studies that were apparently negative, the panel often failed to comment on their shortcomings, and chose instead to treat them as if they were reliable, as if true negatives.

Moreover, that skewed pattern of interpretation is especially puzzling when notice is taken of the fact that almost all apparently negative studies were funded by organisations with vested commercial interests and every single one of the positive studies were non-commercially funded. That pattern undermines the panel's claim that its judgements are based on and only on scientific evidence. If they had been, its conclusion would have been very different.

Of course none of the studies, whether positive or negative, are perfect; all studies are characterised by some imperfections. What is striking about the panel's treatment of the negative and positive studies is that it unremittingly highlights and criticises the shortcomings of all the positive studies, often invoking guesswork rather than evidence, yet generously neglecting or forgiving almost all of the shortcomings of the negative studies.

This pattern raises a crucial question about whether or not the members of the panel were sufficiently neutral and open-minded, or whether the criteria of inclusion and interpretations might have been biased.

The following tabulation indicates the membership of the panel, and whether or not evidence of possible conflicts of interest is available.

Name of panel members	**Focus of possible conflict in interest: Commercial or Institutional**	**Evidential source**
Fernando Aguilar	Nestle - commercial	Corporate Europe Observatory http://corporateeurope.org/ 15 June 2011
Riccardo Crebelli	ILSI - commercial	Corporate Europe Observatory, http://corporateeurope.org/ 13 Sept 2011
Birgit Dusemund	Member of WG 'Ramazzini Institute study on aspartame - institutional	https://ess.efsa.europa.eu/doi/doiweb/panel/CEF/wg/460523
Pierre Galtier	Member of WG 'Ramazzini Institute study on aspartame - institutional	https://ess.efsa.europa.eu/doi/doiweb/panel/CEF/wg/460523
David Gott	Member of the Secretariat of the Committee on Toxicity - institutional	https://ess.efsa.europa.eu/doi/doiweb/panel/CEF/wg/460523

Ursula Gundert-Remy	ILSI - commercial	Corporate Europe Observatory, http://corporateeurope.org/ 13 Sept 2011
Jürgen Koenig	ILSI - commercial	Corporate Europe Observatory, http://corporateeurope.org/ 15 June 2011
Claude Lambré	Member of WG 'Ramazzini Institute study on aspartame - institutional	https://ess.efsa.europa.eu/doi/doiweb/panel/CEF/wg/460523
Jean-Charles Leblanc	Member of ILSI working group 2006 to 2009 - commercial	CEO 15 June 2011, http://corporateeurope.org/ and http://corporateeurope.org/print/publications/open-letter-ceo-european-food-safety-authority
Alicja Mortensen	Chair of ad hoc WG 'Ramazzini Institute study on aspartame in mice and methanol' - institutional	https://ess.efsa.europa.eu/doi/doiweb/panel/CEF/wg/460523
Pasquale Mosesso		none
Dominique Parent-Massin	Coca Cola - commercial	Corporate Europe Observatory, http://corporateeurope.org/ 15 June 2011 Cf Conference "*entretiens de bichat*" in workshop organised by the communication agency "proteine" on behalf of coca cola on "actuality in food safety of sweeteners"

Ivan Stankovic		none
Paul Tobback	ILSI - commercial	Corporate Europe Observatory, http://corporateeurope.org/ 15 June 2011
Ine Waalkens-Berendsen		none
Rudolf Antonius Woutersen	Expert - WG 'Ramazzini Institute study on aspartame in mice and methanol' - institutional	Source https://ess.efsa.europa.eu/doi/doiweb/panel/CEF/wg/460523
Matthew Wright		none

The information in that table indicates that of the 17 members of the panel, only 4 are not characterised by some relevant conflicts of interest. 7 members of the panel have commercial conflicts of interest, as they do work, or have worked, with commercial organisations with direct commercial interests in aspartame. Furthermore, 6 members of the panel are now employed in, or have been employed by, regulatory institutions that have published documents asserting the safety of aspartame, during the course of their employment; they are therefore characterised by institutional conflicts of interest.

Moreover, Dr Lesley Stanley, who was contracted by EFSA to conduct 'preparatory work for the re-evaluation of aspartame', was a member of the UK's Committee on Toxicity (CoT) from 2001 to 2007, reported to the CoT on the papers published by the Ramazzini Foundation. , (COC/06/S2 – December 2006 Available as http://www.iacoc.org.uk/statements/documents/COC06S2AspartamestatementDec2006_000.pdf)

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Conclusion:
The analysis provided in and substantiated by this report has revealed that with a very few exceptions, almost all studies that have been reported as suggesting that aspartame poses no risks to human health have been treated buy the panel as if robust and reliable by the EFSA panel, while all (ie 100%) of the studies that suggest that consuming aspartame may pose a risk to health were deemed by the panel to be unreliable.

The EFSA panel has portrayed all the apparently positive findings as false positives, most frequently by reference to opportunistic hypotheses rather than by reference to relevant empirical evidence. By contrast the panel has been almost entirely blind to possible false negatives.

The only way in which the conclusion of this report can be sustained, namely that aspartame is unproblematically safe, is firstly by assuming that all apparently 'positive' studies are unreliable, even though none were commercially funded, secondly that all the apparently negative studies are entirely reliable, despite the fact that almost all of which were commercially funded, and thirdly that conflicts of interest are inconsequential. Those three assumptions are however implausible, perverse and unscientific.

EFSA should therefore discount the entire draft report, and convene a new panel composed only of experts who are entirely free of any conflicts of interest, and its work should be supported only by individuals who have no conflicts of interest. The new panel should be asked to review all the evidence, not just some of it, and in way that prioritises the protection of consumer and public health over any commercial or industrial considerations.

The European Commission and the European Parliament should also take responsibility for ensuring that EFSA acts properly to protect consumers rather than assisting the food and chemical industries.

Moreover the European Commission and the European Parliament should meet their responsibilities by ensuring that EFSA acts properly to protect consumers rather than helping the food and chemical industries.

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Appendix 1

The following table identifies each of the 30 documents in the dossier I delivered to the EFSA in the autumn of 2011, and outlines what they show.

1	***Additives: A Guide for Everyone*** **(Penguin Books): Erik Millstone: 1988** Excerpt This document summarises my research into the toxicological and regulatory history of aspartame, as of 1988, and outlines numerous concerns about the safety of aspartame.
2	**Paper published in *The Ecologist*: Erik Millstone: 1994** Several serious concerns about the safety and approval of aspartame were elaborated in this paper.
3	**Chronology: US Senator Howard Metzenbaum's staff: 1986** with subsequent elaborations This is a chronology of some of the main events in the scientific, regulatory and commercial history of aspartame. It highlights key events in the process whereby unreliable evidence came to be submitted, and then accepted by the US regulatory authorities.
4	**Who's Who: Senator Howard Metzenbaum's staff: 1986** Prepared in connection with the failure of the Chicago Federal Attorney's office to convene a Grand Jury to indict G D Searle – the firm that developed aspartame and that gained consent for it to be marketed.

5	**List of documents about the G D Searle testing and approval process: Senator Howard Metzenbaum's staff: 1986** This list indicates the thoroughness with which Metzenbaum's team detailed the shortcomings in the testing and approval processes of aspartame in the USA. Since subsequently the UK, EC/EU and the JECFA all relied on US data, and presumed the adequacy of those data and the review of them by the US authorities, they too suffer from identical problems. **Observations** The scandal about the short-comings in the conduct and reporting of test on aspartame was first uncovered by scientists from the FDA's drug control division. The FDA decided to investigate Aspartame after one of its leading pathologists, Dr Adrian Gross, noticed what he thought was a worrying anomaly in a Searle report on a pharmaceutical product, Flagyl; the summary at the start of Searle's submission did not accurately reflect the detailed data presented in subsequent chapters. The report was returned by Gross to Searle in the expectation that it would be re-submitted with the summary revised to fit the data. Gross was surprised when a fresh submission arrived with data altered to fit the summary! In response, officials from the FDA's Drugs Division made an unannounced investigative visit to Searle's offices and laboratories. In the course of the FDA's investigation 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 they were supposed to be reporting, and consequently may have underestimated the toxicity of the sweetener. In response 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.
6	**Studies in support of safety of aspartame: NutraSweet company: undated, obtained from G D Searle's London representatives in 1987** This document lists all the studies whose data were provided to the UK and US governments (and presumably to JECFA and the SCF too) in support of aspartame. It shows that the key studies whose validity is in question were included in Searle's original dossier.

7	**Establishment Investigation Report (EIR): FDA's initial Searle Task Force: 18 February 1978** This covers several studies conducted with aspartame under contract to Searle by Hazleton Laboratories Inc. based in Virginia. **Observations** Study E77/78 — 30 serious errors noted in the conduct and reporting of that study. Study E32 — 21 serious errors noted Study E28 — 14 serious errors noted Study E27/35 — 16 serious errors noted including (p10): Observation for drug effect records are inconsistent Records for hamster No. N9LM indicate this animal was not alive on October 23 1970, was alive on November 20, was not alive on December 18 and January 15 1971, was alive February 12, and was found dead on February 25 It is difficult to see how any reliance can be placed on studies that have been so poorly conducted and reported.
8	**Final Report: FDA's Bureau of Drugs Searle Task Force: 24 March 1976** This reviews serious inadequacies in the general conduct of toxicity tests, conducted both by Searle and by a sub-contractor Hazleton Laboratories. **Observations** "At the heart of FDA's regulatory process is its ability to rely upon the integrity of the basic safety data submitted by sponsors of the regulated products. Our investigation clearly demonstrates that, in the case of the G.D. Searle Company, we have no basis for such reliance now…Through our efforts, we have uncovered serious deficiencies in Searle's operations and practices which undermine the basis for reliance on Searle's integrity in conducting high quality animal research to accurately determine or characterise the toxic potential of its products." (page 1) Under Recommendation #1 the report states: "…the Bureau of Foods should make a determination on the disposition of the Aspartame studies currently under official FDA seal at Searle and Hazleton Laboratories." (page 8)

9	**Memo on reviewing aspartame studies: Dr Adrian Gross, US FDA: 4 November 1976** available at http://www.dorway.com/gross1.html This is a memo from Dr Adrian Gross of the US FDA to one of his superiors, Carlton Sharp, concerning the FDA's intention to contract out to the Universities Associated for Research and Education in Pathology Inc (or UAREP) the responsibility for reviewing 12 of the 15 safety studies on aspartame that the initial FDA investigation had indicated were problematic. The memo indicates that Gross doubted that the UAREP had the relevant expertise, and that he doubted the wisdom of having G D Searle pay for the UAREP's work. He was concerned that G D Searle might influence the conduct and reporting of the UAREP's work. In the event, Gross's concerns turned out to be well-grounded. The first few pages, including the Table of Contents, of the UAREP report appear as item 15 in the current dossier. **Observations** The memo shows that not only were the tests on aspartame unreliable, but that serious questions arise in connection with the steps taken by the FDA ostensibly to 'validate' the Searle studies.
10	**Letter from Richard Merrill, then FDA's Chief Counsel in Washington, to Samuel Skinner, then US Federal Attorney in Chicago: 10 January 1977** (the discussion of aspartame starts on page 17) Richard Merrill instructs Samuel Skinner to convene a Grand Jury to investigate Searle's conduct in respect of both aspartame and aldactone. **Observations** The eventual failure of Skinner and his colleagues to convene a Grand Jury, because the Statute of Limitations expired, was a crucial step and institutional failure in the aspartame saga.
11	**Internal memo from Samuel Skinner to his subordinates: 8 March 1977** Skinner indicates that he has decided to recuse (i.e. excuse) himself from the Searle investigation because he had been invited to join the law firm Sidley and Austin, which was representing G D Searle. **Observations** Under those circumstances Skinner had no choice but to withdraw from the Searle investigation, but the development contributed to delays that eventually resulted in the time limit set under the Statute of Limitations expiring before the next stage of due process could be completed.

12	**Bressler Report – first part: 18 July 1977** An Establishment Investigation Report (EIR) covering the period from 2 March 1977 to 8 July 1977 that documents in great detail serious inadequacies in two of the studies (E5 and E89) conducted on aspartame, both intended to evaluate the embryotoxicity and teratogenic potential of aspartame when administered orally to albino rats (E5) and to mice (E89). **Observations** Establishment Investigation Reports were a tool developed by the FDA, before the rules on Good Laboratory Practice were established, if serious concerns were raised about the ways in which experiments had been conducted and/or reported.
13	**Bressler Report – second part: 15 August 1977** available at http://www.dorway.com/bressler.txt An Establishment Investigation Report (EIR) that documents in great detail the serious inadequacies in a pivotal test on DKP (diketopiperazine), which is one of aspartame's breakdown products. Establishment Investigation Reports were then a tool developed by the FDA, before the rules on Good Laboratory Practice were established, if serious concerns were raised about the ways in which experiments had been conducted and/or reported. **Observations** The study in question (PD 988S73, SC-19192) was a 115 week rodent oral carcinogenicity study on diketopiperazine, a decomposition product of aspartame. The main findings of the 77 page EIR are summarised in Appendix 1 below.

14	**Internal FDA memo from the Bureau of Foods Task Force to the Acting Director of the FDA Bureau of Foods, Howard R. Roberts: 28 September 1977** Along with its appendices, this memo provides an analysis that was supposed to summarise the two Bressler Reports. This memo is, however, a curious document because, despite the numerous problems highlighted by Bressler and his colleagues, it states on page 3 that: "The differences observed and documented...are not of such a magnitude that they would significantly alter the conclusions of the studies" and "...the three studies appear to be authentic." These conclusions are puzzling because they gloss over many of the issues raised in, and appear to be inconsistent with many of the facts recorded in, the two Bressler Reports. The reason for this apparent anomaly is explained in the quotation from Dr Jacqueline Verrett that follows. **Observations** In May 1987 Dr Jacqueline Verrett, one of the signatories to the 28 September 1977 memo, provided the following explanation. This is from her statement on the record at a hearing of the US Senate Committee on Labor and Human Resources (3rd November 1987, item 24, page 383 et seq.) Her comments explain the divergence between the summary and conclusions of the Bureau of Foods Task Force Report and the evidence on which it was supposed to have been based. "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. [i.e. the Bureau of Food Task Force was instructed to ignore the difference between the way in which the study was supposed to have been conducted and the way in which it had actually been conducted and also to ignore the failure to mix the test compound properly into the feed of the laboratory animals.] 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 that 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. Our remit was limited to a comparison of the Bressler data against the original data. 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."
15	**UAREP report: Table of contents: 18 November 1977** These are just the first few pages of the 1,062 pages document. An entire copy could be provided if the FSA finds it difficult otherwise to obtain a copy. The Table of Contents lists those studies that the UAREP reviewed. **Observations** A critique of the UAREP Report is provided by Dr Adrian Gross, the FDA pathologist, in his letters to Senator Metzenbaum which are included in the record of the US Senate Committee on Labor and Human Resources, 3 November 1987. (See item 25 below, p.430 et seq, especially pages 435 – 6) The texts of those letter are available at http://www.dorway.com/gross.txt

16	Two letters from Dr Adrian Gross to Senator Howard Metzenbaum, both dated 3 November 1987, and reproduced in the record of US Senate Committee on Labor and Human Resources (item 25 below) available at http://www.dorway.com/gross.txt These letters discuss, amongst other things, the short-comings of the review by the UAREP of toxicity studies on aspartame
17	**Report of the Public Board of Inquiry (PBOI) into aspartame: 30 September 1980** In 1979, in an attempt to resolve the controversy once and for all, the FDA set up a Public Board of Inquiry that published its conclusions in October 1980. **Observations** The PBOI confined itself to examining two questions, both relating to Aspartame's possible effects on the brain. On brain damage resulting in mental retardation, it took the view that Aspartame consumption would not pose an increased risk of mental retardation. On brain tumours, 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. The conclusion of the document states that "The Board has not been presented with proof of a reasonable certainty that aspartame is safe for use as a food additive under its intended conditions of use." (p. 49)
18	**Copy of an internal FDA memo from Robert Condon, an FDA toxicologist: 19 May 1981** Robert Condon explains to his superior why he is not convinced that aspartame had been shown to be safe in respect of the risk of brain tumours. **Observations** Condon highlighted the postive results in a study (also known as E33/34) in female rats, inadequacies in the conduct of studies E70 and E78, and the limited power of those studies. This document was written after the PBOI had reported but before the then Commissioner at the FDA, A H Hayes, approved aspartame for use in the USA. It indicates that Hayes did not have the endorsement of some of his staff for his decision, and indicates why not.

19	**Memo from Dr Douglas Park, a senior FDA toxicologist, to his superior: 19 May 1981** Dr Park argues that the evidence of the brain tumour risk from aspartame was equivocal, but he explains that the information provided to the PBOI was, in some key respect, inaccurate, and that the correct information would have reinforced their concerns about the risks that aspartame consumption could pose. He concluded that aspartame had not been shown to be safe, and recommended against approval. **Observations** On 15 July 1981, Arthur Hull Hayes, US FDA commissioner, overruled the Public Board of Inquiry and approved aspartame, initially for dry products, asserting that aspartame has been shown to be safe. In September 1983, ex-Commissioner Hayes joined Burston-Marsteller, Searle's public relation firm. On 8 July 1983, Acting FDA commissioner, Mark Novitch, approved aspartame for use in carbonated beverages.
20	**Letter from Professor Richard Wurtman at the Massachusetts Institute of Technology to the *New England Journal of Medicine*: 18th August 1983 pp. 429 – 430)** Professor Richard Wurtman explains why he expects the introduction of aspartame into soft drinks to risk provoking a range of adverse neurological symptoms.
21	**Senator Howard Metzenbaum's *Nutrasweet Bill*: 1 August 1985** This is the Bill that Senator Howard Metzenbaum presented to the US Senate on 1st August 1985. This document provides a careful review of some of the key issues in this extensive controversy.
22	**Senator Metzenbaum's letter to the Chair of the Senate Judiciary Committee: 3 February 1986** Senator Metzenbaum sets out his concerns about the conduct of several members of the staff of the US Federal Attorney's Office in Chicago in relation to their investigation into Searle's affairs and their dealing with Sidley and Austin.
23	**Letter from Samuel Molinary, then the Vice President, Regulatory Affairs of the Nutrasweet Company, to Erik Millstone; 20 April 1987** Samuel Molinary confirms that the three key studies referred to in the Bressler Reports items 12 and 13 had never been repeated. He contended that they did not need to be repeated, but that is a key issue that this dossier serves to contest.
24	**Text of an American newspaper article by Gregory Gordon: 12 October 1987** The article reviews some recently emerged concerns relating to the possible acute toxicity of aspartame in human consumers.

25	**Cover page and table of contents of the Senate Committee hearings** The whole document is 530 pages long, so this dossier does not provide a copy of the entire document, although if the EFSA has difficulties gaining access to this material I could assist.
26	**Paper by Prof John Olney of Washington University, St Louis and his colleagues in the *Journal of Neuropathology and Experimental Neurology*: November 1996** The authors analysed cancer statistics from the US National Cancer Institute covering a sample of approximately 10% of the US population for the period from 1975 to 1995. **Observations** The authors found that the introduction of aspartame into the USA, into dry goods in 1981 and soft drinks in 1983, was followed by an abrupt increase in the reported incidence of brain tumours. The change was most noticeable between 1984 and 1985, and it corresponded to approximately 1,500 extra cases of brain cancer per year in the USA. Their second main finding was that there had also been a marked change in the incidence of particular types of brain tumours, with a reduction in the proportion of a relatively less aggressive (and often preliminary) type of tumour (astrocytomas) and a sharp increase in the incidence of a far more aggressive (and all too often terminal) type of tumour (glioblastomas). The investigators argued that the reported changes in tumour incidence were unlikely to have been artefacts of improvements in diagnostic technologies. The introduction and rapid diffusion of computerised tomography in the early to mid- 1970s, and of magnetic resonance imaging technology in the early to mid-1980s, certainly improved diagnostic precision. But they contend that the impact of those innovations upon the reported incidence of these central nervous system (CNS) tumours had fully worked their way through before aspartame was introduced. Before those imaging technologies were introduced, it was far harder to diagnose brain cancer. Consequently, it was often not until tumours developed into glioblastomas that they were diagnosed, and a relatively high portion of tumours at the earlier astrocytoma stage went undetected. When the imaging technologies were introduced, brain tumours tended to be detected at the earlier stage, and consequently in the late 1970s the number of reported astrocytomas went up, while the number of glioblastomas exhibited a corresponding decline. After aspartame was introduced, however, the opposite pattern can be observed. The incidence of glioblastomas rose sharply, and starting in the late 1980s the number of astrocytomas declined even more sharply. Since those latter changes run counter to the direction which could be attributed to the introduction of better diagnostic technologies, it is hard to see how the reported changing tumour incidence could be ascribed to innovations in diagnosis. If the apparent increase in overall incidence had been due to improved diagnostics, then we should expect a marked change in post-diagnostic survival rates, but no such change was evident. Olney and his colleagues suspect aspartame to be implicated in the aetiology of the extra cases of brain cancer for three main reasons. Firstly, the type of CNS tumour found to be increasing most rapidly in the USA is the same kind of lesion as was found in one of the animal studies conducted on aspartame in the 1970s. Secondly Olney and colleagues also drew attention to the results of a study by Shephard et al published in 1993. (Shephard S. E. et al, 'Mutagenic activity of peptides and the artificial sweetener aspartame after nitrosation', *Food and Chemical Toxicology*, 1993, Vol. 31, pp. 323-329) thereby indicating a biochemical mechanism that could account for a tumourogenic effect, and thirdly epidemiological evidence apparently confirming the predictions previously derived from animal and *in vitro* studies.

27	Paper by Shephard S. E. et al, 'Mutagenic activity of peptides and the artificial sweetener aspartame after nitrosation', *Food and Chemical Toxicology*, 1993, Vol. 31, pp. 323-329 Shephard and colleagues attempted to simulate *in vitro* the conditions that can occur in the human digestive tract, and in particular the conditions that result in the nitrosation of dietary ingredients. They reported that the nitrosated aspartame had significant mutagenic action. **Observations** This evidence may be important because it suggests not only a mechanism through which aspartame could exert a carcinogenic action, but also why the interval between the compound's introduction and the emergence of evidence indicating increased brain cancer rates appears to have been so brief. Olney et al also suggested that aspartame may reasonably be suspected of responsibility because the other main possible candidates for responsibility, such as ionising radiation, smoke inhalation, pesticides, electromagnetic fields and various other chemicals were gradually introduced over recent decades rather than all at once in the early 1980s. Exposures to those potential hazards are, furthermore, occupationally linked and it is hard to see how they could explain why males and females seem to be equally affected. If Olney's hypothesis is to be substantiated, it may be helpful to analyse several long-term brain cancer time-series data sets for other countries covering the period both before and since aspartame was introduced. That has proved difficult because while aggregate brain cancer statistics are readily available, information on tumours types is hard to obtain. If aspartame were to act by modifying an already present or nascent brain cancer, we should expect its impact to vary in different countries in ways which depend on the age structure of the consumers of this sweetener and their patterns of consumption. Anecdotal evidence suggests that a far larger proportion of 50 to 70 year old Americans consume aspartame-sweetened products than is the case in the UK or in other European countries. According to Sebastian Bizzari et al of the American Dietetic Association, US residents account for about 75% of all the aspartame consumed in the world, and therefore the evidence from the USA is likely to be clearer than from other countries. (Bizzari et al, 'Position of the American Dietetic Association: Use of Nutritive and Nonnutritive Sweeteners', *Journal of the American Dietetic Association*, Vol 104 No 2, Feb. 2004, p. 263; available at http://www.webdietitians.org/Print/8474_adap0598.cfm)

28	**Paper by Soffritti and his colleagues in the *European Journal of Oncology*: July 2005** In July 2005 Soffritti et al reported evidence that aspartame induced lymphomas and leukaemias in rats, in a consistent dose-related manner. **Observations** This study is crucial because, for many years, critics of the original Searle studies have argued that the original studies that were flawed had never been repeated. The study conducted by Soffritti and his colleagues at the Fondazione Ramazzini, was initiated precisely because the pivotal studies on aspartame toxicity had been so poorly conducted in the first place, and incompetently evaluated. It therefore serves to fill a crucial gap in our scientific knowledge about the toxicity of aspartame. The Ramazzini study used a larger sample of laboratory rodents than the sum of the sizes of the samples of rodents used in all the previous chronic toxicity long-term feeding studies. In these new circumstances, it is now appropriate to conclude that sufficient information has now emerged to indicate that we can now be confident that aspartame is not acceptably safe. While there were quite possibly some shortcomings in the studies conducted by the Fondazione Ramazzini they were far less serious than those that characterized the initial studies conducted by Searle and Hazleton laboratories in the 1970s. To continue to treat the Searle as Hazleton data as reliable but the Fondazione Ramazzini data as unreliable is profoundly unscientific.
29	**Press Release from the European Food Safety Authority: 14 July 2005** This EFSA press release is in response to the publication of the study by Soffritti et al (item 27). The document includes the statement: "EFSA has already held initial discussions with the scientists concerned and will ask its Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC), as a matter of high priority, to review these results, **in the context of the previous extensive safety data available on aspartame**." (emphasis added). **Observations** The phrase emboldened for emphasis in this quotation suggests that the approach being taken by EFSA and by the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food is predicated on the assumption that the results of the Soffritti study can and should be juxtaposed to 'previous safety data'. The analysis implied by this commentary and the dossier of documents that it accompanies is that the previous data do not reliably indicate safety, and therefore that those previous data do not provide an appropriate counter-weight to the findings of the study by Soffritti et al.

30	**Press Release from the Food Standards Agency: 14 July 2005** This FSA press release also responded to the publication of the study by Soffritti et al. **Observations** This too is predicated on the assumption that the data from previous studies can be treated as reliable, while the analysis implied by this commentary and the dossier of documents that it accompanies is that such an assumption is problematic and misleading.