From: Mark Gold [mgold@shelltown.net]
Sent: Sunday, January 12, 2003 11:15 PM
To: fdadockets@oc.fda.gov
Subject: Docket # 02P-0317 Recall Aspartame as a Neurotoxic Drug: File #7: Aspartame History

Subject: Docket # 02P-0317

To: FDA Dockets Submittal

From: Mark D. Gold
Aspartame Toxicity Information Center
12 East Side Dr., Suite 2-18
Concord, NH 03301
603-225-2110

Date: January 12, 2002

Please find below Evidence File #7: Aspartame History

Preapproval "Research" & History of Aspartame

Q. I have been told that there American Medical Association's (AMA) Council on Scientific Affairs reviewed countless preapproval studies and found that they failed to reveal toxic side-effects. Is that true?

A. The AMA council simply repeated what was said by a politically appointed FDA official. Unfortunately, they didn't do any serious research on the subject.

While the "research" performed by the aspartame industry after approval is abyssmal, the *preapproval* "research" was *much* worse. Despite this fact, FDA officials essentially "sold out" to the manufacturer and approved the junk.

In order to fully understand the disasterous preapproval process, it is necessary to highlight important events relating to aspartame in each year since it was invented. This will be done below. It starts out slowly, but please stick with it past 1976 when the preapproval experiment horror stories will begin.

1964

The development of new pharmaceuticals was the focus of research at the international pharmaceutical company, G.D. Searle and Company (Farber 1989, page 29). A group working on an ulcer drug was formed including Dr. Robert Mazer, James Schlatter, Arthur Goldkemp and Imperial Chemical. In particular, they were looking for an inhibitor of the

gastrointestinal secretory hormone gastrin (Stegink 1984a, page 3).

1965

In 1965, while creating a bioassay, an intermediate chemical was synthesized -- aspartylphenylalanine-methyl-ester (aspartame). In December of 1965, while James Schlatter was recrystalling aspartame from ethanol, the mixture spilled onto the outside of the flask. Some of the powder got onto his fingers. Later, when he licked his fingers to pick up a piece of paper, he noticed a very strong sweet taste. He realized that the sweet taste might have been the aspartame. So, believing that the dipeptide aspartame was not likely to be toxic, he tasted a little bit and discovered its sweet taste (Stegink 1984a, page 4). The discovery was reported in 1966, but there was no mention of the sweetness (Furia 1972).

1969

The investigators first reported the discovery of the artificial sweetener in the Journal of the American Chemical Society stating (Mazur 1969):

> "We wish to report another accidental discovery of an organic compound with a profound sucrose (table sugar) like taste . . . Prelminary tasting showed this compound to have a potency of 100-200 times sucrose depending on concentration and on what other flavors are present and to be devoid of unpleasant aftertaste."

In 1969, former Commissioner of the FDA, Dr. Herbert L. Ley was quoted as follows (Griffin 1974):

> "The thing that bugs me is that people think the Food and Drug Administration (FDA) is protecting them -- it isn't. What the FDA is doing and what the public thinks it's doing are as different as night and day."

1970

The discovery of aspartame is reported in the well-known publication, Science (Cloninger 1970).

G.D. Searle approached Dr. Harry Waisman, Biochemist, Professor of Pediatrics, Director of the University of Wisconsin's Joseph P. Kennedy Jr. Memorial Laboroatory of

Mental Retardation Research and a respected expert in phenylalanine toxicity, to conduct a study of the effects of aspartame on primates. The study was initiated on January 15, 1970 and was terminated on or about April 25, 1971. Dr. Waisman died unexpectedly in March, 1971.

Seven infant monkeys were given aspartame with milk. One died after 300 days. Five others (out of seven total) had grad mal seizures. The actual results were hidden from the FDA when G.D. Searle submitted its initial applications (Stoddard 1995a, page 6; Merrill 1977; Graves 1984, page S5506 of Congressional Record 1985a; Gross 1976b, page 333 of US Senate 1976b).

G.D. Searle denied knowledge of or involvement with the initiation, design or performance of the study. Yet, the false results were submitted to the FDA like the rest of the 150 G.D. Searle studies (on aspartame and other products), bearing a Searle Pathology-Toxicology project number. Both Dr. Waisman and G.D. Searle were responsible for the study design. A number of false statements were made by G.D. Searle including that the animals were unavailable for purchase for autopsy after the termination of the study.

Neuroscientist and researcher John W. Olney found that oral intake of glutamate, aspartate and cysteine (in free form -- unbound to protein such as aspartate in aspartame), all excitotoxic amino acids, cause brain damage in mice (Olney 1970).

An internal G.D. Searle memo layed out the strategy for getting aspartame approved (Helling 1970):

> At this meeting [with FDA officials], the basic philospohy of our approach to food and drugs should be to try to get them to say "Yes," to rank the things that we are going to ask for so we are putting first those questions we would like to get a "yes" to, even if we have to throw some in that have no significance to us, other than putting them in a yes saying habit.
>
> We must create affirmative atmosphere in our dealing with them. It would help if we can get them or get their people involved to do us any such favors. This would also help bring them into subconscious spirit of participation.

The FDA banned the sweetener cyclamate. Robert Scheuplein,

who was the acting Director of FDA's Toxicological Services Center for Food Safety and Applied Nutrition was quoted as saying "the decision was more a matter of politics than science." (Stoddard 1995a, page 7)

1971

Ann Reynolds, a researcher who was hired by G.D. Searle and who has done research for the Glutamate (MSG) Association, confirmed aspartame's neurotoxicity in infant mice (Reynolds 1971).

Dr. John W. Olney informed G.D. Searle that aspartic acid caused holes in the brains of mice. G.D. Searle did not inform the FDA of this study until after aspartame's approval. None of the tests submitted by G.D. Searle to the FDA contradicted these findings (Olney 1970, Gordon 1987, page 493 of US Senate 1987).

1972

FDA Toxicologist Dr. Adrian Gross came upon some irregularities in the submitted tests of the G.D. Searle drug Flagyl. G.D. Searle did not respond for another two years. Their response raised serious questions about the validity of their tests (Gross 1975, page 35; Schmidt 1976b, page 6).

1973

On March 5, 1973, G.D. Searle's petition to the FDA for approval to market aspartame as a sweetening agent was published in the Federal Register (1973).

On March 21, 1973 the MBR report was submitted to G.D. Searle.

> Background
> In August of 1970, G.D. Searle conducted two 78-week toxicity studies on rats for what was to become a best-selling heart medication, Aldactone. One study was conducted at G.D. Searle and one at Hazelton Laboratories. In March 1972, the rats for autopsied and the pathology slides were analyzed. For confirmation of the results, G.D. Searle sent the slides to Biological Research, Ltd. where board certified pathologist, Dr. Jacqueline Mauro examined the data. She discovered that the drug appeared to induce tumors in the liver, testes,

> and thyroid of the rats. The report submitted to G.D. Searle by Dr. Mauro was known as the MBR Report.

These statistically significant findings were confirmed by G.D. Searle's Mathematics-Statistics Departement. Instead of submitting these alarming findings to the FDA, G.D. Searle contracted with another pathologist, Dr. Donald A. Willigan. He was given 1,000 slides to examine. The Willigan Report was more to G.D. Searle's liking because it revealed a statistically significant increase in thyroid and testes tumors, but not in liver tumors. Liver tumors are of much more concern to the FDA. The Willigan Report was immediately submitted to the FDA. G.D. Searle did not disclose the MBR Report to the FDA until August 18, 1975, 27 months after it had been given to G.D. Searle (Schmidt 1976b, page 14, Merrill 1977, page S10828-S10831).

At first, G.D. Searle claimed that they did not submit the MBR Report to the FDA because of an "oversight." Later, they claimed that Dr. Mauro's MBR report was not submitted because they did not like the terminology Dr. Mauro used in evaluating the thyroid slides. They claimed that her inaccurate terminology in this case showed that Dr. Mauro was unreliable as a pathologist. Yet, G.D. Searle never notified Dr. Mauro of any questions and on June 1, 1973, they wrote to MBR and stated that the report "looks just fine" (Merrill 1977).

The FDA Commissioner from 1972 to 1976, Alexander Schmidt, M.D. felt that "Superficially, it seemed like, if there would ever be a safe kind of product, that would be it. The idea that two naturally-occurring amino acids could harm someone in relatively small amounts...." (Mullarkey 1992, page 15)

In an FDA memorandum dated September 12, 1973, Martha M. Freeman, M.D. of the FDA Division of Metabolic and Endocrine Drug Products addressed the adequecy of the information submited by G.D. Searle in their petition to approve aspartame (Freeman 1973):

> "Although it was stated that studies were also performed with diketopiperazine [DKP] an impurity which results from acid hydrolysis of Aspartame, no data are provided on this product."

Commenting on one particular single dose study:

> "It is not feasible to extrapolate results of such single dose testing to the likely condition of use of Aspartame as an artificial sweetener."

It is important to note that Dr. Freeman pointed out the inadequency of single-dose tests of aspartame as early as 1973. Since then, the NutraSweet Company has flooded the scientific community with single-dose studies.

> "Chemistry - No information is provided other than formulae for Aspartame and its diketo-piperazine."

> "Pharmacology - Reference is made to 2 year rat studies, but no data are provided on acute or chronic toxicity."

> "Clinical - No protocols nor curriculum vitae information are provided for the 10 completed clinical studies. Results are reported in narrative summary form, and tabulations of mean average values only. No information is given as to the identity of the reporting labs, methodology (except rarely), or normal values. (Reported units for several parameters cannot be verified at this time.)

> "No pharmacokinetic data are provided on absorption, excretion, metabolism, half-life; nor bioaviliability of capsule vs. food-additive administration."

Dr. Freeman concludes:

> "1. The administration of Aspartame, as reported in these studies at high dosage levels for prolonged periods, constitutes clinical investigational use of a new drug substance."

> "2. The information submitted for our review is inadequate to permit a scientific evaluation of clinical safety."

She went on to recommend that marketing of aspartame be contingent upon proven clinical safety of aspartame. The FDA Bureau of Foods rejected Dr. Freeman's recommendation (Graves 1984, page S5498 of Congressional Record 1985a).

Construction of a large aspartame manufacturing plant in Augusta, Georgia was halted. It was thought that aspartame's uncertain regulatory future was the main reason for the stopping of construction (Farber 1989, page 47). In the 1973 G.D. Searle Annual Report, an executive stated that

"commercial quanities of the sweetener will be supplied from the enlarged facility of Ajinomoto." Ajinomoto is the inventor and main producer of the food additive MSG.

1974

Ninety of the 113 aspartame studies which were submitted by G.D. Searle to the FDA were conducted in the early to mid-1970's. All of the tests that were described by the FDA as "pivotal" were conducted during this time. Eighty percent of these tests were conducted by G.D. Searle or by their major contractor, Hazleton Laboratories, Inc. (Graves 1984, page S5497 of Congressional Record 1985a).

Dr. J. Richard Crout, the acting director of the FDA Bureau of Drugs stated that "The information submitted for our review was limited to narrative clinical summaries and tabulated mean values of laboratory studies. No protocols, manufacturing controls infromation or preclinical data were provided. Such deficiencies in each area of required information precluded a scientific evaluation of the clinical safety of this product...." (Mullarkey 1992, page 23)

Dr. John Olney and Consumer Interest attorney, James Turner, Esq. met with G.D. Searle to discuss the results of Olney's experiments. G.D. Searle representatives claim that Olney's data raises no health concerns (Stoddard 1995a, page 7).

The FDA approved aspartame for limited use on July 26, 1974. The allowable uses included free-flowing sugar substitute, tablets for sweetening hot beverages, cereals, gum, and dry bases (Farber 1989, Federal Register 1974). It was not approved for baking goods, cooking, or carbonated beverages. This approval came despite the fact that FDA scientists found serious deficiencies in all of the 13 tests related to genetic damage which were submitted by G.D. Searle.

In August 1974, before aspartame could go on the market, Dr. John Olney, James Turner, and Label Inc. (Legal Action for Buyers' Education and Labeling) filed a formal objection stating that they believe aspartame could cause brain damage. They were particularly worried about aspartame's effects on children (Graves 1984, page S5498 of Congressional Record 1985a; Federal Register 1975, Olney

1987, page 3).

G.D. Searle's responses to queries about the testing of their drug Flagyl, serious and unexpected side effects from other drugs they developed, and information from Dr. John Olney's studies started a controversy within the FDA as to the quality and validity of G.D. Searle's test of aspartame and pharmaceuticals (Graves 1984, page S5498 of Congressional Record 1985a).

1975

In July 1975, the FDA Commissioner, Dr. Alexander Schmidt appointed a special Task Force to look at 25 key studies for the drugs Flagyl, Aldactone, Norpace, and the food additive aspartame. Eleven of the pivotal studies examined involved aspartame. All of the studies whether conducted at G.D. Searle or Hazleton Laboratories were the responsibility of the Pathology-Toxicology Department at G.D. Searle. (Gross 1987a, page 430 of US Senate 1987). The special Task Force was headed by Philip Brodsky, FDA's Lead Investigator and assisted by FDA Toxicologist, Dr. Adrian Gross. The Task Force was especially interested in "pivotal" tests as described in an article from Common Cause Magazine by Florence Graves (Graves 1984, page S5499 of Congressional Record 1985a):

> "Before the task force had completed its investigation in 1976, Searle had submitted the vast majority of the more than 100 tests it ultimately gave the FDA in an effort to get aspartame approved. These included all tests ever described as 'pivotal' by the FDA. About half the pivotal tests were done at Searle; about one-third were done at Hazleton Laboratories. 'Pivotal' tests include long-term (two-year) tests such as those done to determine whether aspartame might cause cancer. Former FDA commissioner Alexander Schmidt said in a recent interview that if a pivotal test is found to be unreliable, it must be repeated 'Some studies are more important than others, and they have to be done impeccably,' Schmidt said."

G.D. Searle executives admited to "payments to employees of certain foreign governments to obtain sales of their products." (Searle 1975)

On July 10, 1975, Senator Edward Kennedy chaired a hearing on drug-related research before the Senate Subcommittee on Health of the Committee on Labor and Public Welfare (US Senate 1975). Preliminary reports of discrepancies discovered about G.D. Searle were discussed. The findings of the FDA Task Force were later presented at further hearings on January 20, 1976 (US Senate 1976a) and April 8, 1976 (US Senate 1976b).

On December 5, 1975, Dr. John Olney and James Turner waived their right to a hearing at the suggestion of the FDA General Counsel after the FDA and G.D. Searle agreed to hold a Public Board Of Inquiry (PBOI) (Federal Register 1975, page 286, Mullarkey 1994b, page 5-6).

On December 5, 1975, the FDA put a hold on the approval of aspartame due to the preliminary findings of the FDA Task Force. The Public Board of Inquiry is also put on hold (Mullarkey 1994b, page 5-6; Federal Register 1975). The evidence of the aspartame pivotal studies were protected under FDA seal on December 3, 1975 (Sharp 1975).

G.D. Searle had invested 19.7 million dollars in an incomplete production facility and 9.2. million dollars in aspartame inventory. On December 8, 1975, stockholders filed a class action lawsuit alledging that G.D. Searle had concealed information from the public regarding the nature and quality of animal research at G.D. Searle in violation of the Securities and Exchange Act (Farber 1989, page 48).

1976

On January 7, 1976, G.D. Searle submited to the FDA their proposal for the adoption of "Good Laboratory Practices" (Buzzard 1976b). G.D. Searle's input was used in FDA's adoption of Good Laboratory Practices.

In March 1976, the FDA Task Force completed a 500-page report with 15,000 pages of exhibits (80-page summary) to the FDA after completing their investigation (Schmidt 1976c, page 4 of US Senate 1976b).

A preliminary statement about the breadth of the investigation from FDA Toxicologist and Task Force team member, Dr. Andrian Gross before the US Senate (Gross 1987a, page 1-2):

> "Practices that were noted in connection with any given such study were quite likely to have been noted also for other studies that were audited, and this was a situation which was in no way unexpected: after all, the set of all such studies executed by that firm from about 1968 to the mid-1970's were conducted in essentially the same facilities, by virtually the same tehnicians, professional workers and supervisors, and the nature of such studies does not differ much whether a food additive or a drug product is being tested for safety in laboratory animals. It is in this sense, therefore, that the overall conclusion summarized at the beginning of the Searle Task Force Report have relevance to all the studies audited in 1975 (whether they had references to aspartame or to any of the six drug products of Searle's) and, by extension, to the totality of experimental studies carried out by that firm around that time -- 1968 to 1975."

A few of the conclusions of the FDA Task Force (Gross 1987a, page 2-3):

> "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 regulated products. Our investigation clearly demonstrates that, in the (case of the) GD Searle Company, we have no basis for such reliance now."
>
> "We have noted that Searle has not submitted all the facts of experiments to FDA, retaining unto itself the unpermitted option of filtering, interpreting, and not submitting information which we would consider material to the safety evaluation of the product . . . Finally, we have found instances of irrelevant or unproductive animal research where experiments have been poorly conceived, carelessly executed, or inaccurately analyzed or reported."
>
> "Some of our findings suggest an attitude of disregard for FDA's mission of protection of the public health by selectively reporting the results of studies in a manner which allay the concerns of questions of an FDA reviewer."
>
> "Unreliability in Searle's animal research does

not imply, however, that its animal studies have provided no useful information on the safety of its products. Poorly controlled experiments containing random errors blur the differences between treated and control animals and increase the difficulty of discriminating between the two populations to detect a product induced effect. A positive finding of toxicity in the test animals in a poorly controlled study provides a reasonable lower bound on the true toxicity of the substance. The agency must be free to conclude that the results from such a study, while admittedly imprecise as to incidence or severity of the untoward effect, cannot be overlooked in arriving at a decision concerning the toxic potential of the product."

A few of the relevant findings summarized from various documents describing the FDA Task Force Report:

a. "Excising masses (tumors) from live animals, in some cases without histologic examination of the masses, in others without reporting them to the FDA." (Schmidt 1976c, page 4 of US Senate 1976b) Searle's representatives, when caught and questioned about these actions, stated that "these masses were in the head and neck areas and prevented the animals from feeding." (Buzzard 1976a)

   "Failure to report to the FDA all internal tumors present in the experimental rats, e.g., polyps in the uterus, ovary neoplasms as well as other lesions." (Gross 1987a, page 8).

b. G.D. Searle "stored animal tissues in formaldehyde for so long that they deteriorated." (Gordon 1987, page 496 of US Senate 1987; US Schmidt 1976c, page 25, 27 of US Senate 1976b)

c. "Instead of performing autopsies on rhesus monkeys that suffered seizures after being fed aspartame, the company had financed a new monkey seizure study with a different methodology that showed no problems." (Gordon 1987, page 496 of US Senate 1987)

d. "Reporting animals as unavailable for necropsy when, in fact, records indicate that the animals were available but Searle choose not to purchase them." (Schmidt 1976c, page 5 of US Senate 1976b)

e. Animals which had died were sometimes recorded as being alive and vica versa. "These include approximately 20 instances of animals reported as dead and then reported as having vital signs normal again at subsequent observation periods." (Gross 1985, page S10835)

f. "Selecting statistical procedures which used a total number of animals as the denominator when only a portion of the animals were examined, thus reducing the significance of adverse effects." (Schmidt 1976c, page 4 of US Senate 1976b)

g. G.D. Searle told the FDA that 12 lots of DKP were manufacturered and tested in one study, yet only seven batches were actually made. (Gross 1985, page S10835)

h. "Significant deviations from the protocols of several studies were noted which may have compromised the value of these studies . . . In at least one study, the Aspartame 52 weeks monkey study, the protocol was written after the study had been initiated." (Gross 1985, page S10835)

i. "It is significant to note that the Searle employee responsible for reviewing most of the reproduction studies had only one year of prior experience, working on population dynamics of cotton tail rabbits while employed by Illinois Wildlife Service. In order to prepare him for this title of 'Senior Research Assistant in Teratology' (fetal damage) Searle bought him books to read on the subject and also sent him to a meeting of the Teratology Society. This qualified him to submit 18 of the initial tests to the FDA, in addition to training an assistant and 2 technicians. He certainly must have kept them busy because Searle claimed that 329 teratology examinations were conducted in just 2 days. He estimated that he himself examined about 30 fetuses a day, but officials for the Center for Food and Applied Nutrition could never determine how that was possible." (Stoddard 1995a, page 9; Graves 1984, page S5500 of Congressional Record 1985a)

j. "In each study investigated, poor practices, inaccuracies, and discrepancies were noted in the antemortem phases which could compromise the study." (Gross 1985, page S10836 of

Congressional Record 1985b)

k. "Presenting information to FDA in a manner likely to obscure problems, such as editing the report of a consulting pathologist . . . Reporting one pathology report while failing to submit, or make reference to another usually more adverse pathology report on the same slide." (Schmidt 1976c, page 4-5 of US Senate 1976b)

l. Animals were not removed from the room during the twice per month exterminator sprayings. (Gross 1985, page S10836 of Congressional Record 1985b)

m. Often the substance being tested which was given to the animals was not analyzed or tested for homogeneity. "No records were found to indicate that any treatment mixtures used in the studies were ever tested or assayed for pesticide content . . . Running inventory records for either treatment mixtures or the test compounds used in treatment mixtures are not maintained." (Gross 1985, page S10836 of Congressional Record 1985b)

n. In the Aspartame (DKP) 115 week rat study the written observations of the pathology report was changed by the supervising pathologist, Dr. Rudolph Stejskal even though he was not physically present during the autopsies and could not have verified the observations of the pathologist who did perform the autopsies. The pathologist who did perform some of the autopsies had no formal training for such procedures. (Gross 1985, page S10837 of Congressional Record 1985b)

o. "Contrary to protocol, slides were not prepared of this [unusual lesions from the Aspartame (DKP) study) tissue for microscopic examinstions . . . ." (Gross 1985, page S10837 of Congressional Record 1985b)

p. "In the Aspartame 46 weeks hamster study, blood samples reported in the submission to FDA as 26 week values (for certain specified animals) were found by our investigators as being, in fact, values for different animals which were bled at the 38th week. Many of the animals for which these values were reported (to the FDA) were dead at the 38th week." (Gross 1985, page S10838 of Congressional

Record 1985b)

"It is apparent from the report, that the Appendix portion contains all the individual (animal) values of clinical lab data available from the raw data file. A selected portion of these values appears to have been used in computing group means (which were reported to the FDA). It is not clear what criteria may have been used for selecting a portion of the data or for deleting the others in computing the means (reported to the FDA)." (Gross 1985, page S10838 of Congressional Record 1985b)

q. "Searle technical personnel failed to adhere to protocols, make accurate observations, sign and date records, and accurately administer the product under test and proper lab procedures." (Farber 1989, page 109)

r. [There were] "clerical or arithmetic errors which resulted in reports of fewer tumors." (Schmidt 1976c, page 27 of US Senate 1976b)

s. [G.D. Searle] "delayed the reporting of alarming findings." (Schmidt 1976c, page 27 of US Senate 1976b)

FDA Toxicologist and Task Force member, Dr. Andrian Gross stated (Wilson 1985):

"They [G.D. Searle] lied and they didn't submit the real nature of their observations because had they done that it is more than likely that a great number of these studies would have been rejected simply for adequacy. What Searle did, they took great pains to camouflage these shortcomings of the study. As I say filter and just present to the FDA what they wished the FDA to know and they did other terrible things for instance animals would develop tumors while they were under study. Well they would remove these tumors from the animals."

FDA Lead Investigator and Task Force Team Leader, Phillip Brodsky described the 1975 FDA Task Force members as some of the most experienced drug investigators. He went on to state that he had never seen anything as bad as G.D. Searle's studies (Graves 1984, page S5499 of Congressional Record 1985a).

The report quoted a letter written to G.D. Searle on July 15, 1975 from its consultant in reproduction and teratology, Dr. Gregory Palmer, in regards to a review of some of G.D. Searle's repreductive studies submitted to the FDA (Gross

1985, page S10838 of Congressional Record 1985b):

> "Even following the track you did, it seems to me you have only confounded the issue by a series of studies most of which have severe design deficiencies or obvious lack of expertise in animal management. Because of these twin factors, all the careful and detailed examination of fetuses, all the writing, summarization and resummarization is of little avail because of the shaky foundation."

G.D. Searle officials noted that Dr. Palmer did not look at all of the teratology studies (Searle 1976b, page 21). However, there is no credible evidence that would lead a reasonable person to believe that the studies which were not presented to Dr. Palmer were much better. In fact, the evidence shows that it is very likely that all of the studies were abyssmal.

The FDA Commissioner at the time, Alexander Schmidt stated (Graves 1984, page S5497 of Congressional Record 1985a):

> "[Searle's studies were] incredibly sloppy science. What we discovered was reprehensible."

Dr. Marvin Legator, professor and director of environmental toxicology at the University of Texas and the pioneer of mutagenicity testing at the FDA from 1962 to 1972 was asked by Common Cause Magazine to review the FDA investigation results of G.D. Searle's tests (Graves 1984, page S5498 of Congressional Record 1985a):

> "[All tests were] scientifically irresponsible [and] disgraceful. I'm just shocked that that kind of sloppy [work] would even be sent to FDA, and that the FDA administrators accepted it. There is no reason why these tests couldn't have been carried out correctly. It's not that we are talking about some great scientific breakthrough in methodology."

Senator Edward Kennedy at the April 8, 1976 hearings before the Senate Subcommittee on Labor and Public Welfare stated (Kennedy 1976):

> "The extensive nature of the almost unbelievable range of abuses discovered by the FDA on several major Searle products is profoundly disturbing."

In January, 1976, G.D. Searle defended their results by claiming (Searle 1976a, page 5-6):

> "In all of the studies at Searle which have been examined by the FDA in its investigation, the scope of the material being considered included seven years of observation, from 1968 to date, in 57 studies involving more than 5,700 animals with over 228 million observations and calculations."

However, their deliberate misconduct and "lies" (as put by FDA Investigator, Dr. Adrian Gross) invalidated their experiments for the following reasons:

1. Many of the problems with the studies included horrendous experimental designs, questions regarding dosage given, loss of animal tissue and data, etc., etc., which invalidates entire experiments and causes what they claim to be 4 million observations and calculations per study (average) to become irrelevant.

2. Only the key aspartame studies were looked at. It is almost a certainty that the non-key aspartame studies were equally flawed. Therefore, this would invalidate the "hundreds of millions" of observations and calculations made during these studies.

3. The difference between a study showing no statistical difference and a significant statistical difference is often only a few observations or calculations. Therefore, had the myriad of other serious experimental errors not occurred (as detailed above), the observation and calculation mistakes in each experiment investigated would, by themselves, invalidate most of the key studies.

4. It is highly unlikely that the FDA Investigative teams found all of the problems with G.D. Searle's studies. G.D. Searle seemed so intent on covering up their misconduct, that it is quite likely that they were able to hide many of the problems from the FDA.

A series of poorly conceived, flawed studies funded by G.D. Searle were published in Volume 2 (1976) of the Journal of Toxicology and Environmental Health. An Associate Editor of this scientific journal was Robert G. McConnell, the Director of G.D. Searle's Department of Pathology and Toxicology (the department responsible for monitoring the quality of G.D. Searle's pre-approval tests investigated by the 1975 FDA Task Force). Mr. McConnell's story continues later in 1977. Another G.D. Searle employee, Carl R. Mackerer was an editor of the journal. Another editor of the journal was Thomas R. Tephly, the person responsible for conducting a series of badly flawed blood methanol and

formate measurements in NutraSweet-funded studies over the last 15 years.

In July 1976, the FDA decided to investigate 15 key aspartame studies submited by G.D. Searle in which the 1975 FDA Task Force discovered problems. Three (3) of the studies were investigated at the FDA (E5, E77/78, E89) by a 5-member Task Force headed by FDA veteran Inspector, Jerome Bressler (Graves 1984, page S5499 of Congressional Record 1985a; Gordon 1987, page 497 of US Senate 1987; Farber 1989, page 110).

On August 4, 1976, G.D. Searle representatives met with the FDA and convinced them to allow G.D. Searle to hire a private agency, University Associated for Education in Pathology (UAREP), and pay them $500,000 to "validate" the other 12 studies (Gordon 1987 page 498 of US Senate 1987)

According the FDA Commissioner during the early 1980s, Arthur Hull Hayes, the UAREP investigation was to "make sure that the studies were actually conducted."

As described by Florence Graves (1984, page S5500 of Congressional Record 1985a):

> "The pathologists were specifically told that they were not to make a judgment about aspartame's safety or to look at the designs of the tests. Why did the FDA choose to have pathologists conduct an investigation when even some FDA officials acknowledged at the time that UAREP had a limited task which would only partially shed light on the validity of Searle's testing? The answer is not clear.
>
> "Dr. Kenneth Endicott, Director of UAREP, said in an interview that the FDA had 'reasons to suspect' that Searle's tests 'were not entirely honest.' Because the FDA 'had doubts about [Searle's] veracity,' Edicott said, officials wanted UAREP 'to determine whether the reports were accurate.'
>
> "FDA scientist Dr. Adrian Gross, in a letter to an FDA official, said, 'speaking as a pathologist, it seemed questionable that the group could do the kind of comprehensive investigation that was required. He pointed in particular to a variety of issues that needed to be investigated. He said some of these would involved closely questioning administrators and lab technicians about their

> practices. Since many important issues that should be investigated 'have nothing to do with pathology,' he said, only trained FDA investigators were qualified to do a comprehensive evaluation of the testing. . . .
>
> "Meanwhile, an interview with Endicott indicates that Adrian Gross was right: the pathologists couldn't--and didn't--carry out a comprehensive review. . . . As former FDA Commissioner Alexander Schmidt put it in a recent interview, UAREP looked at the slides to determine whether they had been misrepresented, but didn't look at the conduct of the experiments in depth. The 1975 [FDA] task force investigation looked at the conduct of the experiments in depth, but did not look at the slides. . . . Endicott agreed . . . 'We could only look at what was there--the tissues.'

The findings of this investigation where released in the Bessler Report in August 1977 (see below).

1977

Donald Rumsfeld, who was a former member of the U.S. Congress and the Chief of Staff in the Gerald Ford Administration, was hired as G.D. Searle's President. Attorney James Turner, Esq. alledged that G.D. Searle hired Rumsfeld to handle the aspartame approval difficulties as a "legal problem rather than a scientific problem." (Gordon 1987, page 497 of US Senate 1987).

As layed out by Mary Nash Stoddard (Stoddard 1995a, page 11), Rumsfeld hired:

> John Robson as Executive Vice President. He was a former lawyer with Sidley and Austin, Searle's Law Firm and also served as chairman of the Civil Aeronautics Board, which was then connect to the Department of Transportation.
>
> Robert Shapiro as General Counsel. He is now head of Searle's NutraSweet Division. He had been Robson's Special Assistant at the Department of Transportation.
>
> William Greener, Jr., as Chief Spokesman. He was a former spokesman in the [Gerald] Ford White House.

Donald Rumsfeld is now on the Board of Directors of the Chicago Tribune which recently wrote a glowing article about the NutraSweet Company (Millman 1995, Mullarkey 1995).

On January 10, 1977, FDA Chief Counsel Richard Merrill recommended to U.S. Attorney Sam Skinner in a 33-page letter detailing violations of the law that a grand jury be set up to investigate G.D. Searle. In the letter, Merrill stated (Merril 1977, page S10827 of Congressional Record 1985b):

> "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 conceailing 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."

All of the G.D. Searle studies were abyssmal as discussed earlier. However, there were two studies where the violations of the law appeared to be especially flagrant. The two studies cited by Merrill were the 52-week toxicity study on infant monkeys performed by Dr. Waisman which G.D. Searle withheld key information from the FDA and the 46-week toxicity study of hamsters where G.D. Searle had taken blood from healthy animals at the 26th week and claimed that the tests had actually been performed at the 38th week. Many of the animals from which G.D. Searle claimed had blood drawn from were actually dead at the 38th week. See earlier discussion for references.

On January 26, 1977, G.D. Searle's law firm, Sidley & Austin, requested a meeting with U.S. Attorney Samuel Skinner before a grand jury is convened (Gordon 1987 page 497 of US Senate 1987, Mullarkey 1994b, page 6-7). One representative of Sidley & Austin at that meeting was Newton Minow who is currently on the Board of Diretors at the Chicago Tribune (Gordon 1987, page 497 of US Senate 1987; Mullarkey 1995).

On March 8, 1977, in a confidential memo to aides, while he was supposed to be pushing for fraud indictments against G.D. Searle, U.S. Attorney Samuel Skinner stated that he had begun preliminary employment discussions with G.D. Searle's law firm Sidley & Austin (Gordon 1987, page 497 of US Senate 1987; Mullarkey 1994b, page 7).

On April 13, 1977, a U.S. Justice Department memo urged U.S. Attorney Samuel Skinner to proceed with grand jury investigations of G.D. Searle. The memo points out that the Statute of limitations on prosecution would run out shortly (October 10, 1977 for the Waisman monkey study and December 8, 1977 for the hamster study) (Mullarkey 1994b, page 7).

Samual Skinner withdrew from the G.D. Searle case and Assistant U.S. Attorney William Conlon was then assigned to the Grand Jury investigation (Gordon 1987, page 497 of US Senate 1987).

On July 1, 1977, U.S. Attorney Samuel Skinner left his job to work for the G.D. Searle law firm Sidley & Austin. Thomas Sullivan was appointed as Samuel Skinner's successor (Gordon 1987, page 497 of US Senate 1987).

Assistant U.S. Attorney William Conlon convened a grand jury, but he let the Statute of Limitations run out on the aspartame charges (Gordon 1987, page 497 of US Senate 1987). Fifteen months later, Conlon accepted a job with the law firm representing G.D. Searle, Sidley & Austin (Gordon 1987, page 497 of US Senate 1987).

Robert McConnell was the Director of G.D. Searle's Department of Pathology and Toxicology which oversaw most of the aspartame research. Mr. McConnell was named in Richard Merrill's letter to U.S. Attorney Samuel Skinner. According to McConnell's attorney, his client was awarded a $15,000 bonus and asked to take a 3-year sabbatical (for which he received $60,000/year) because he was a "political liability." (Gordon 1987, page 496 of US Senate 1987)

Philip Brodsky, the Lead Investigator for the orginal FDA Task Force looking into G.D. Searles studies retired. He stated that his reason for retiring was the disclosure of the 1975 FDA Task Force findings before the U.S. Congress (Sen Kennedy hearings in 1976) had become "politicized." As Gregory Gordon put it in the UPI Investigative article (Gordon 1987, page 496 of US Senate 1987):

> "He said the main witnesses, Searle executives and top FDA officials uninvolved in the investigation gave 'the wrong answers to the wrong questions . . . They didn't even let the experts answer the questions.'"

In August 1977, the Bressler Report pertaining to three key aspartame studies, E5, E77/78 and E89, was released. Some of the findings from the three studies reviewed by the Bressler-led FDA Task Force include (Mullarkey 1994b, page 11, 48; Farber 1989, page 110-112; Verrett 1987, page 385 of US Senate 1987):

a. In one study, 98 of the 196 animals died but were not autopsied until as much as one year later. Because of the delay, much of the animal tissue could not be used and at least 20 animals had to be excluded from postmortem examinations.

b. The original pathology sheets and the pathology sheets submitted to the FDA showed differences for 30 animals.

c. One animal was reported alive at week 88, dead from week 92 through week 104, alive at week 108, and finally dead at week 112.

d. An outbreak of an infectious disease was not reported to the FDA.

e. Tissue from some animals were noted to be unavailable for analysis on the pathology sheets, yet results from an analysis of this "unavailable" tissue was submitted to the FDA.

f. There was evidence that the diet mix was not homogeneous allowing the animals to eat around the test substance. This evidence included a picture and statements by a lab technician.

g. Fifteen fetuses from animals in one experiment were missing.

h. Sections from the animals were too thick for examination.

i. There was no documentation on the age or source of the test animals.

j. There was no protocol until one of the studies was well underway.

k. Animals were not permanently tagged to prevent mixups.

1. Some laboratory methods were changed during the study, but not documented.

A G.D. Searle pathologist referring to the DKP study was quoted by investigators as saying (Graves 1984, page S5500 of Congressional Record 1985a):

> "You should have seen things when this study was run -- there were five studies being run at one time -- things were a mess!"

The leader of the Task Force, Jerome Bressler, was quoted as saying (Gordon 1987, page 497 of US Senate 1987):

> "The question you have got to ask yourself is: Because of the importance of this study, why wasn't greater care taken? The study is highly questionable because of our findings. Why didn't Searle, with their scientists, closely evaluate this, knowing fully well that the whole society, from the youngest to the elderly, from the sick to the unsick . . . will have access to this product."

Immediately after the Bressler Report was released, H.R. Roberts, Director of the FDA's Bureau of Foods created a 5-person task force to review the Bressler Report. The review was done by a team at the Center for Food Safety and Applied Nutrition (CFSAN report). H.R. Roberts would leave the FDA to become a vice president of the National Soft Drink Association in 1978. FDA Toxicologist, Jacqueline Verrett was appointed the Senior Scientist of the Bureau of Foods Task Force.

On September 28, 1977, H.R. Roberts, Director of the FDA's Bureau of Foods received a report from a Bureau of Foods Task Force which claimed that G.D. Searle's studies they reviewed appeared to be authentic (meaning that they were actually conducted) (Mullarkey 1994b, page 8).

For each of the major discrpancies found by the Bressler-led Task Force -- those listed above and many others -- there was a comment in the FDA Bureau of Foods Report minimizing the problem. It seemed that no matter how serious the mistakes were, the FDA Bureau of Foods was determined to accept the studies by G.D. Searle.

The experimental errors as described above were so bad that it proved difficult to minimize all of the major errors in these key studies. In some cases, the best that the CFSAN could do was to say that "The Task Force could find no

evidence that this was a deliberate attempt to influence the study." or "It could not be determined if the results would have been altered...." (Farber 1989, page 111, GAO 1987, Appendix IV).

The Senior Scientist of the FDA Bureau of Foods Task Force, Jacqueline Verrett had left the FDA when she openly discussed the Task Force with UPI Investigative Reporter, Gregory Gordon (Gordon 1987, page 497 of US Senate 1987):

> "Jacqueline Verrett, the senior scientist on the review team, said members were barred from stating opinions about the research quality. 'It seemed pretty obvious that somewhere along that line they (bureau officials) were working up to a whitewash,' she said. 'I seriously thought of just walking off of that task force.' Verrett, now a private consultant, said that she and other members wanted to 'just come out and say that this whole experiment was a disaster and should be disregarded.'

In her testimony before the U.S. Senate, Dr. Verrett stated the following (Verrett 1987):

> "This authentication was hence intended to verify that the submitted data had not been altered; that it reflected the actual outcome of the study, and that it did not change substantially, particularly in a statistical sense, the various parameters from which the conclusion of safety had been derived.
>
> "Our analysis of the data in this manner revealed that in these three studies, there were really no substantial changes that resulted, although in numerous instances, a definitive answer could not be arrived at because of the basic inadequacies and improper procedures used in the execution of these studies.
>
> "I would like to emphasize the point that we were specifically instructed not to be concerned with, or to comment upon, the overall validity of the study. This was to be done in a subsequent review, carried out at a higher level.
> . . . .
> "It would appear that the safety of aspartame and its breakdown products has still not been satisfactorily determined, since many of the flaws cited in these three studies were also present in all of the other studies submitted by Searle.
> . . . .
> "Well, they told us in no uncertain terms that we

were not to comment on the validity of it. And I hoped, although having been there at that point for 19 years, I should have known better, that there really would be an objective evaluation of this beyond the evaluation that we did.

"I do not feel that that was done, based on what I have read in the GAO report that I have looked at and so forth. They definately did not objectively evaluate these studies, and I really think it should have been thrown out from day one.

"We were looking at a lot of little details and easy parameters in this study, when the foundation of the study, the diet and all of these other things, were worthless. We were talking about the jockey when we should have been talking about the horse, that he had weak legs. It is built on a foundation of sand."

The FDA general counsel wrote a letter to Consumer Attorney, James Turner, Esq. responding to Mr. Turner's concern about the quality and validity of G.D. Searle's experiments. The FDA stated, "The Public Board of Inquiry on aspartame should provide a vehicle for definitive resolution, at least for those studies about which you are most concerned." (Graves 1984, page S5498 of Congressional Record 1985a). As will be discussed later, Dr. John Olney and James Turner, Esq. were not allowed to have the quality and validity of the G.D. Searle studies considered at the Public Board of Inquiry.

1978

On December 13, 1978, UAREP submited its results of their analysis of 12 of G.D. Searle's aspartame studies. UAREP stated in their report that "no discrepancies in any of the sponsor's reports that were of sufficient magnitude or nature that would compromise that data originally submitted." (Farber 1989, page 33) Remember, the Director of UAREP pointed out in an interview that their pathologists did not conduct a comprehensive review of the studies, they only looked at the animal tissues (Graves 1984, page S5500 of Congressional Record 1985a).

As it turns out, UAREP pathologists who examined the test results were discovered to have missed and withheld negative findings from the FDA (Gross 1987b, page 2-5). In some cases, they completely missed cancerous brain tumors when analyzing the slides. In addition, some of the slides that were to be examined by UAREP pathologists were missing even though they where supposed to have been kept under "FDA

seal." (Olney 1987, page 6-7) FDA Toxicologist Adrian Gross stated that the UAREP review "may well be interpreted as nothing short of a whitewash." (Farber 1989, page 114). Given that the UAREP review results was so biased in favor of G.D. Searle, one wonders why the FDA would allow a company being investigated for fraud to pay $500,000 and hire an outside entity to "validate" their studies.

Even though the UAREP report was biased, there were numerous instances in that report which demonstrated that G.D. Searle had not submitted even marginally accurate findings to the FDA of their pre-approval aspartame tests. For example, in one study, twelve animals actually had cancerous brain tumors, yet UAREP reported to the FDA that only three animals had such tumors (Gross 1987b, page 3-4).

1979

In March of 1979, the FDA somehow concluded that G.D. Searle's aspartame studies could be accepted. They decide to convene the Public Board of Inquiry (PBOI) which was agreed to by Dr. John Olney and Attorney James Turner more than four years earlier (Federal Register 1979).

In April of 1979, the FDA outlined the specific questions which were to be addressed by the PBOI. The FDA limited the scope of the PBOI to (Federal Register 1981):

a. Whether the ingestion of aspartame either alone or together with glutamate poses a risk of contributing to mental retardation, brain damage, or undesireable effects on neuroendocrine regulatory systems.

b. Whether the ingestion of aspartame may induce brain neoplasms (tumors) in the rat.

c. Based on answer to the above questions.

   (i) Should aspartame be allowed for use in foods, or, instead should approval of aspartame be withdrawn?

   (ii) If aspartame is allowed for use in foods, i.e., if its approval is not withdrawn, what conditions of use and labeling and label statements should be required, if any?

Dr. John Olney, G.D. Searle, and the FDA's Bureau of Foods were allowed to nominate scientists for the 3-person PBOI

panel (Farber 1989, page 34, Federal Register 1981, page 38286).

It is important to note that the scope of the review was very limited in light of all of the various adverse reactions reported to the FDA. The PBOI also disallowed any discussion of the validity of the pre-approval experiments because it accepted the word of certain FDA officials that these experiments had been "validated." Finally, the PBOI was told not to consider aspartame in beverages, only in dry goods.

In June of 1979, the acting FDA Commissioner, Sherwin Gardner selected the 3-person Public Board of Inquiry. The panelists were Peter J. Lampert, M.D., Professor and Chairman, Department of Pathology, University of California (San Diego), Vernon R. Young, Ph.D., Professor of Nutritional Biochemistry, M.I.T., and Walle Nauta, M.D., Ph.D., Institute Professor, Department of Psychology and Brain Science, M.I.T.

Dr. John Olney strongly objected to the Commissioner's selection of one of the panelists, Dr. Vernon Young, on grounds of conflict of interest and lack of qualifications (Olney 1987, page 3). Dr. Young had written nonaspartame-related articles in collaboration with G.D. Searle scientists (Brannigan 1983, page 196). In addition, Dr. Olney stated that the question of aspartic acid's neurotoxicity should be looked at by a neuropathologist and that Dr. Young was unqualified since his field was Nutrition and Metabolism. Dr. Olney's objections were overruled by acting FDA Commissioner Sherwin Gardner and the panelists who he objected to was assigned to study the issue of aspartic acid toxicity.

One of the PBOI members, Dr. Walle Nauta stated (Graves 1984, page S5498 of Congressional Record 1985a):

> "It was a shocking story we were told [about Searle's animal testing] but, there was no way we could go after it. We had absolutely no way of knowing who was right. We had to take the FDA's word."

Dr. Nauta stated that he would have "definately" considered other tests and factors if he had known that aspartame was planned for use in soft drinks (Graves 1984, page S5503 of Congressional Record 1985a).

1980

The Public Board Of Inquiry voted unanimously to reject the

use of aspartame until additional studies on aspartame's potential to cause brain tumors could be done. The PBOI was particularly concerned about experiment E33/34 where 320 rats received aspartame and a much higher percentage of animals in the aspartame group developed tumors than in the control group (Brannigan 1983, page 196). In addition, the PBOI was concerned about experiment E70 where 80 rats received aspartame. Both the aspartame group and the control group had an unusually high number of tumors, leading one to suspect that both groups were actually given aspartame (Federal Register 1981).

The PBOI did not believe that aspartic acid presented a neurotoxic hazard. Yet, Dr. Olney pointed out that (Olney 1987, page 3):

> "[Dr. Young had a] lack of qualification" and that he "based his decision on a consideration of [aspartic acid] alone without regard to the real issue, i.e., is it safe to add [aspartic acid] to the large amounts of [glutamic acid/MSG] that are already adultering the food supply?"

In addition, the "conservative" safety plasma level of aspartic acid used by Dr. Young was the level at which half the animals developed brain damage (Brannigan 1983, page 197). These errors by Dr. Young throw the question of safety of aspartic acid as part of aspartame into doubt. We will address this issue in more detail in a later section.

1981

On January 21, 1981, the day after Ronald Reagan takes office as U.S. President, G.D. Searle reapplied for the approval of aspartame. G.D. Searle submits several new studies along with their application. It was believed that Reagan would certainly replace Jere Goyan, the FDA Comissioner. G.D. Searle president, Donald Rumsfeld's connections to the Republican party were also thought to play a part in Searle's decision to reapply for aspartame's approval on the day after Ronald Reagan was inaugurated (Gordon 1987, page 499 of US Senate 1987).

According to a former G.D. Searle salesperson, Patty Wood-Allott, G.D. Searle president, Donald Rumsfeld told his salesforce that, if necessary, "he would call in all his markers and that no matter what, he would see to it that aspartame would be approved that year." (Gordon 1987, page 499 of US Senate 1987)

In March of 1981, a 5-member panel of scientists was established by the FDA Commissioner Jere Goyan to review the issues raised by the PBOI (Gordon 1987, page 498 of US Senate 1987; Mullarkey 1994b, page 8).

In April 1981, Arthur Hull Hayes, Jr. was appointed FDA Commissioner by Ronald Reagan (Graves 1984, page S5502 of Congressional Record 1985a).

On May 18, 1981, three of the scientists in the 5-member panel sent a letter to the panel lawyer, Joseph Levitt discussing their concerns about aspartame. Those three scientists were Satva Dubey (FDA Chief of Statistical Evaluation Branch), Douglas Park (Staff Science Advisor), and Robert Condon (Veterinary Medicine). Dubey thought that the brain tumor data was so "worrisome" in one study that he could not recommend approval of aspartame (Gordon 1987, page 495 of US Senate 1987). In another study, Dubey said that key data appeared to have been altered (Gordon 1987, page 499 of US Senate 1987).

In his UPI Investigation, Gregory Gordon went on to describe the unusual events that followed (Gordon 1987, page 499 of US Senate 1987):

> "[Douglas] Park said that [panel lawyer Joseph] Levitt hurried the panel to decide the issue. 'They wanted to have the results yesterday,' he said. 'We really didn't have the time to do the in-depth review we wanted to do.'
>
> "Park said Levitt met frequently with Hayes and 'was obviously getting the pressure to get a resolution and a decision made.'
>
> "With three of five scientists on the commissioner's team opposing approval, it was decided to bring in a toxicologist for his opinion on isolated issues [Barry N. Rosloff]. Goyan said if the decision were his, he never would have enlarged the team. While the panel did not vote, it ended up split 3-3.
>
> "Levitt, who normally would have been expected to draft an options paper spelling out scientific evidence on key issues, took an unusual tack. He circulated an approval recommendation and only backed off when Dubey, Park, and Condon objected, team members said. Levitt said he was not directed

> to draft the approval memo, but did so as a 'tactical' step to break the team's weeks-long impasse by forcing each scientist to state his views. 'It worked, didn't it?' said Levitt, who later was promoted to a post as an executive assistant to the FDA Commissioner."

On July 18, 1981 aspartame was approved for use dry foods by FDA Commissioner Arthur Hull Hayes, Jr. overruling the Public Board of Inquiry and ignoring the law, Section 409(c)(3) of the Food Drug and Cosmetic Act (21 U.S.C. 348), which says that a food additive should not be approved if tests are inconclusive (Federal Register 1981, Farber 1989, page 38). In an article in Common Cause Magazine, Florence Graves states that two FDA officials said that Arthur Hull Hayes, Jr. wanted to push aspartame approval through in order to signal reforms of the Reagan Administration. The "reasoning" behind the FDA Commissioner's decision will be discussed in a later section (Graves 1984, page S5497 of Congressional Record 1985a).

1982

On October 15, 1982, G.D. Searle petitioned the FDA for approval to use aspartame in soft drinks and children's vitamins (Gordon 1987, page 499 of US Senate 1987; Farber 1989, page 38)

On October 1, 1982 an amendment was attached to the Orphan Drug Act (an act which encourages the development of drugs for rare diseases) which modified the U.S. Patent law (Congressional Record 1982). The amendment extended the patent on only one product -- aspartame -- by 5 years, 10 months and 17 days (Gordon 1987, page 504 of US Senate 1987). The amendment did not mention aspartame or G.D. Searle by name and there was no debate or discussion on the amendment.

The amendment was proposed by Senator Howell Heflin, brought up for a vote by Senator Robert Byrd, and pushed through by Representative Henry Waxman and Orrin Hatch. G.D. Searle asked Senator Heflin to sponsor the amendment. Heflin received $9,000 in campaign donations shortly after this amendment was approved from G.D. Searle company executives and their wives. Senator Byrd had received a $1,000 campaign contribution from the CEO of G.D. Searle before the amendment was proposed. Representative Waxman received a $1,500 campaign contribution from the soft drink political action committee including $500 before the amendment was

proposed. Senator Hatch received $2,500 from the soft drink political action committee prior to his reelection and $1,000 each from Daniel Searle, Wesley Dixon (Daniel Searle's brother-in-law), and William Searle (Gordon 1987, page 506 of US Senate 1987). Senator Hatch repeatedly blocked hearings looking into the safety of aspartame (Gordon 1987, page 506 of US Senate 1987).

It could be argued that the amendment to extend G.D. Searle's patent of aspartame rectified the lost marketing time caused by the FDA investigations. However, it was G.D. Searle's horrendous pre-approval studies which led to the FDA investigations and the delays. Had they performed the studies with any competance, aspartame could have been approved quickly like any other FDA-approved food additive. (Actually, had the studies been done right, it is likely that aspartame would never been approved due to serious adverse reactions.) In addition, the amendment was applicable to one product and cannot be used similarly for other products.

Between 1979 and 1982, four FDA officials who took part in the aspartame approval process went through the FDA revolving door and took jobs in industries that are closely linked with the NutraSweet issue (Gordon 1987, page 498 of US Senate 1987):

1. Mike Taylor was an FDA lawyer who represented the FDA Bureau of Foods at the PBOI and was part of the team that prevented the quality and validity of G.D. Searle's studies from being considered (Gordon 1987, page 498 of US Senate 1987).

2. Sherwin Gardner was the Deputy FDA Commissioner in 1979. In July, 1974, he had signed the initial approval for aspartame's use in dry foods. (This initial approval was later block by objections from James Turner, Esq. and Dr. John Olney.)

   In December, 1979, Sherwin Gardner became a Vice President of Grocery Manufacturers of America, Inc. (GAO 1986). While Mr. Gardner claims that he did not discuss aspartame is his 4 meetings with the FDA within a year of leaving that agency or his 20 meetings with the FDA between 1980 and 1986, the organization he worked for does deal directly with aspartame products. It is unlikely that he would have been rewarded with the job had he called for another delay in approval and proposed that safety tests be conducted independantly in order to protect the public.

3. Stuart Pape was the Health and Human Services (HHS)

Chief Counsel for Foods from October 1976 to March 1979. He served as special assistant to the FDA Commissioner from March 1979 to December 1979. He participated in meetings and discussions on aspartame as well as representing the FDA at the PBOI.

In December 1979, Mr. Pape was given a job by the law firm of Patton, Boggs, and Blow. This law firm provided counself to the National Soft Drink Association (NSDA). Mr. Pape and Howard R. Roberts of the NSDA (who formerly fought for approval of aspartame at the FDA) met with the FDA twice in 1983 where aspartame was discussed. In 1983, the NSDA inexplicably withdrew their objection to aspartame in diet beverage (GAO 1986).

4. Albert Kolbye was the Associate Director of the FDA Bureau of Foods for toxicology.

1983

Acting FDA Commissioner, Mark Novitch approved aspartame for use in carbonated beverages and carbonated beverage syrup bases (Federal Register 1983). FDA Commissioner, Arthur Hull Hayes was out of town the day that the approval was signed, but he worked closely with Mark Novitch on this issue (Gordon 1987, page 499 of US Senate 1987). Ignoring the FDA's own safety standards, they more than doubled the Acceptable Daily Intake (ADI) of aspartame from 20 mg/kg to 50 mg/kg (Metzenbaum 1985).

Shortly after the FDA approval for aspartame in carbonated beverages, FDA Commissioner, Arthur Hull Hayes left the FDA under charges of improprieties, took a a position as the Dean of New York Medical Collage and was hired as an a consultant ($1,000 per day) with G.D. Searle's public relations firm, Burston Marsteller (Gordon 1987, page 499 of US Senate 1987).

On July 8, 1983, Dr. Woodrow Monte, Director of the Science and Nutrition Laboratory at Arizona State University filed a petition objecting to the approval of aspartame based on possible serious adverse effects from the chronic intake of aspartame. Dr. Monte was especially concerned about the chronic intake of methanol (Federal Register 1984). Dr. Monte also filed a petition with the Arizona Department of Health Services to ban aspartame.

On July 8, 1983, James Turner, Esq. filed a peition with the FDA on behalf of himself and Community Nutrition Institute objecting to the approval of aspartame (Federal Register 1984).

Dr. Woodrow Monte, at the suggestion of his lawyer, invested $2,000 in G.D. Searle stock options in order to raise money for his costly legal battles against aspartame. He ended up losing $1,224. His purchasing of the "put options" caused some controversy. Dr. Monte was later accused of conflict-of-interest by G.D. Searle. Dr. Monte's lawyer had told him that he "didn't think there was anything wrong" with purchasing the options. A move that Dr. Monte later called a mistake. (Gordon 1987, page 508 of US Senate 1987)

On November 23, 1983, the FDA denied a request to put the approval on hold "because public interest did not require it." (Federal Register 1984).

1984

On February 17, 1984, the FDA denied Dr. Woodrow Monte and James Turner the opportunity to hold a safety hearing on questions raised in their petition (Federal Register 1984).

G.D. Searle sent a number lobbyists to the State of Arizona including Andrew Herwitz, Arizona Governor Babbitt's former Chief of Staff, Charles Pine, a prominent Arizona lobbyist, Roger Thies, a G.D. Searle lawyer, and David West, a G.D. Searle official (Gordon 1987, page 507 of US Senate 1987; Stoddard 1995a, page 17).

The State of Arizona DHS completed studies showing that aspartame in carbonated beverages can break down into free methanol (among other things) in 99oC temperatures. The amount of methanol which broke down concerned the DHS enough that a ban of aspartame was discussed (Gordon 1987, page 507 of US Senate 1987).

Between August 23, 1984 and September 21, 1984, G.D. Searle officials contributed to the campaign of Arizona House Majority Leader Burton Barr. The Committee to Reelect Barr then gave campaign contributions to a number of state

representatives (Don Aldridge, Karen Miills, Jan Breuer) who all eventually voted of the side of G.D. Searle (Gordon 1987, page 507 of US Senate 1987).

Dr. Woodrow Monte's petition for a hearing regarding banning aspartame in Arizona was rejected (Gordon 1987, page 507 of US Senate 1987).

6,900,000 pounds of aspartame were consumed in the U.S. in 1984 (USDA 1988).

1985

Dr. Richard Wurtman of MIT is quoted as saying that Dr. Gerald Gaull, a G.D. Searle Vice President, came to his laboratory and threatened to veto his funding from the International Life Sciences Institute (ILSI) after Wurtman quit his job as a G.D. Searle consultant and became a NutraSweet opponent (Gordon 1987, page 503 of US Senate 1987).

Dr. Woodrow Monte filed for reconsideration of his petition for a hearing in Arizona. He was granted a hearing scheduled for April 1985 (Gordon 1987, page 507 of US Senate 1987).

In April 1985, in an unusual and secret maneuver, the Arizona legislature removed the text in a Toxic Waste Bill and used it to pass a bill which banned the regulation of FDA-approved food additives (Gordon 1987, page 508 of US Senate 1987). This bill scuttled the hearing that Dr. Monte had been promised.

On May 7, 1985, the U.S. Senate heard testimony relating to an amendment put forth by Senator Howard Metzenbaum requiring the quantity of aspartame to be labelled (Congressional Record 1985a). It is nearly impossible for a person to determine what quantity of aspartame they are ingesting unless it is labelled. Senator Orrin Hatch of Utah led the fight (along with G.D. Searle) against the labelling ammendment. The ammendment was defeated. Those voting against the amendment included:

Abdnor, Armstrong, Baucus, Bentsen, Biden, Bingaman, Boren,

Boschwitz, Bradley, Bumpers, Cochran, Cohen, D'Amato, Danforth, DeConcini, Denton, Dixon, Dole, Domenici, Durenberger, Evans, Ford, Garn, Goldwater, Gore, Gorton, Gramm, Gassley, Hatch, Hawkins, Hecht, Heflin, Heinz, Helms, Hollings, Humphrey, Inouye, Kassebaum, Kasten, Laxalt, Leahy, Levin, Lugar, Mattingly, McClure, McConnell, Mitchell, Murkowski, Nickles, Nunn, Packwood, Pressler, Pryor, Quayle, Riegle, Roth, Rudman, Sasser, Simpson, Stafford, Stevens, Symms, Thurmond, Tribe, Wallop, Warner, Wilson, Zorinsky.

Those voting for the amendment included:

Burdick, Byrd, Chafee, Chiles, Cranston, Dodd, Eagleton, Glenn, Harkin, Hart, Hatfield, Johnston, Kennedy, Kerry, Lautenberg, Long, Mathias, Matsunaga, Melcher, Metzenbaum, Moynihan, Pell, Proxmire, Rockefeller, Sarbanes, Simon, Spector.

On August 1, 1985, Senator Howard Metzenbaum of Ohio introduced a bill entitled "Aspartame Safety Act of 1985" which required quantity labelling of aspartame on food items and mandated that there be a moratorium on new uses of aspartame until independent tests could be conducted under the auspices of the National Institutes of Health (Metzenbaum 1985). Testimony was submitted for the record. The bill was submitted to a Senate committee where it died.

After suffering a $28 million dollar loss in the previous year, selling off 30 subsidaries, and having a suit filed by 780 women claiming that G.D. Searle's intrauterine device caused them pelvic inflammatory disease, G.D. Searle sold out to the chemical company, Monsanto (Gordon 1987, page 509 of US Senate 1987). Monsanto then created the NutraSweet Company as a subsiderary separate from G.D. Searle.

14,400,000 pounds of aspartame were consumed in the U.S. in 1985 (USDA 1988).

1986

Community Nutrition Institute (CNI) filed suit against the FDA in District Court claiming that the FDA did not follow proper procedure in approving aspartame for beverages and that they should have held a public hearing before giving final approval (Farber 1989, page 39). After the District Court dismissed their suit and the D.C. Circuit Court of

Appeals denied their request for a hearing stating that they failed to "raise any material issues of fact that require the FDA to grant a hearing," CNI stated:

> ...where the holding of a public hearing is no longer a responsible part of the food additive process, the F.D.A. and the appeals court have increased the likelihood that unsafe food additives will reach the market.

In July 1986, the U.S. General Accounting Office (GAO) published the results of an investigation of five former government employees involved in the aspartame approval process who took jobs linked to the aspartame industry (GAO 1986). While these former employees' actions were not illegal, it is a good example of how the U.S. Government and especially the FDA "revolving door" helps certain powerful companies have near complete control over governmental actions. Government employees will give industry whatever it wants (and the public be damned). Then many of these employees will be rewarded with high-paying industry jobs. Some of those people will then end up back in government in order to do more favors for their industry friends -- even if it means destroying people's lives and health. The inner-city gangs are not the only place where morally corrupt individuals operate with near impunity.

15,700,000 pounds of aspartame were consumed in the U.S. in 1986 (USDA 1988).

1987

The United Press reported on October 12, 1987 that more than 10 federal officials involved in the NutraSweet decision took jobs in the private sector linked to the aspartame industry (Gordon 1987, page 495 of US Senate 1987).

On November 3, 1987 a hearing was held in a U.S. Senate Committee to address the issue of aspartame safety and labelling (US Senate 1987). Senator Orin Hatch successfully block any labelling requirements.

In June 1987, the U.S. General Accounting Office (GAO) published the results of an investigation which looked into whether the FDA followed its required approval process (GAO

1987). The report concluded:

> "Because FDA followed its required approval process in approving aspartame and monitors adverse reactions and ongoing aspartame research, GAO is making no recommendations."

It is important to note that the author of the report specifically stated on the first page:

> "We did not evaluate the scientific issues raised concerning the studies used for aspartame's approval or FDA's resolution of these issues, nor did we determine aspartame's safety. We do not have such scientific expertise."

The GAO seemed only interested in whether the FDA took the legally appropriate steps, not whether or not the FDA's decisions were based on the facts or made any sense.

- They were not interested in the fact that CFSAN's evaluation of the Bressler report was a "whitewash" in the words of the head scientist of the CFSAN team.

- They were not interested in the severe reactions suffered by many of the animals in the preapproval studies.

- They were not interested in the countless, major flaws in the preapproval studies as described earlier.

- They were not interested in the fact that the FDA Commissioner, who later consulted for the G.D. Searle Public Relations firm (at $1,000 per day), over-ruled the Public Board of Inquiry (PBOI) experts and over-ruled his own chosen scientific experts to approve aspartame.

- They were not interested that the FDA decided to allow G.D. Searle to pay UAREP $500,000 to "validate" 15 of their studies.

They were only interested in whether the legally required steps were taken. Even with the limited scope of the GAO investigation, they made numerous factual errors in their report, some of which are detailed in the letter from fromer FDA Investigator and Toxicologist Dr. Andrian Gross presented before the U.S. Senate in 1987 (Gross 1987b, page 11). Dr. Gross concludes:

> "Although in their report the GAO expresses the view that the FDA 'followed its required process in approving aspartame (for marketing)' I would sharply disagree with such evaluation. Although

> the FDA may have gone through the motions or it may have given the appearance of such a process being in place here, the people of this country expect and require a great deal more from that agency charged with protecting their public health:- in addition to mere facade or window-dressing on the part of the FDA, they require a thorough and scientifically based evaluation by the Agency on the safety of the products it regulates.
>
> "Unfortunately this has clearly not been the case here. And without this kind of assurance, any such 'process' or dance represents no more than a farce and a mockery of what is truly required."

An estimated 17,100,000 pounds of aspartame were consumed in the U.S. in 1987 (USDA 1988). NutraSweet stopped providing consumption data to the USDA after 1987. It is much easier for NutraSweet scientists to create inaccurate aspartame consumption figures when the total number of pounds sold is not publically available, or is inaccurate when it is given out publically.

1988

In August 1988, aspartame was approved for use in Brazil (Monsanto 1990). Thanks to a massive advertising campaign, at the end of 1990, 150 products were sweetened exclusively by aspartame.

1990

In May 1990, Nutrasweet opened a production facility in Sao Jose dos Campos, Brazil (Monsanto 1990). There was no diet foods in Brazil in the 1980s. Unfortunately, part of NutraSweet's efforts "to build a diet segment from zero" in Brazil will likely lead to many people in Brazil obsessing about the weight and appearance which in turn often leads to eating disorders and other psychological problems. At the same time, NutraSweet is beginning to dose the population with their slow poison.

1991

NutraSweet joined with its long-time partner, Ajinomoto Co. Inc. of Japan to begin building an aspartame manufacturing plant in Gravelines, France (Monsanto 1991).

The NutraSweet Company began a project to develop a new artificial sweetener, called "Sweetener 2000" which is said to be approximately 10,000 times sweeter than sugar. The chemical composition of this sweetener was not detailed in Monsanto's Annual Report. NutraSweet's plan is to get this new sweetener to the market by the end of the decade (Monsanto 1991).

1992

NutraSweet signed agreements with the Coca-Cola Co. and PepsiCo Inc. "stipulating The NutraSweet Company as their preferred supplier of aspartame (Monsanto 1992).

NutraSweet stated that one of their options for increases sales in the carbonated soft drink market is to prepare "higher-concentration formulations that use more aspartame" (Monsanto 1992).

The FDA approved the NutraSweet Company's application to market aspartame in bulk form. NutraSweet markets the product under the name "NutraSweet Spoonful" (Monsanto 1992).

The patent for aspartame expired on December 14, 1992 opening up the market to other companies such as Holland Sweetener Company (Monsanto 1992).

1993

In mid-1993, NutraSweet and long-time partner, Ajinomoto Co. of Japan began producing aspartame from the new production facility in Gravelines, France (Monsanto 1993).

NutraSweet began a joint venture with Nestle Mexico to bring aspartame to Mexico (Monsanto 1993).

NutraSweet began to explore other aspartame marketing opportunities in Mexico (Monsanto 1993).

1994

NutraSweet introduced tabletop aspartame products to Mexico, Hungary, Uganda, Ecuador, Romania, Uruguay, and Paraguay (Monsanto 1994).

Aspartame's net sales outside of the U.S. accounts for 10 percent of all net sales (Monsanto 1994).

As detailed by investigative journalist Gregory Gordon (Gordon 1996):

> "Between the early 1980s and 1994, scientists at the National Institutes of Environmental Health Sciences (NIEHS) proposed at least four times that the government's leading program for toxicology research fund such studies."
>
> "The government scientists said they wanted the National Toxicology Program to conduct animal studies to resolve questions about the sweetener's cancer risks."
>
> "After each of these "nominations," NIEHS officials elected not to pursue the research at the urging of FDA officials, who said they were satisfied with industry-sponsored research that found no health risks."

NutraSweet announced plans to market aspartame tabletop sweeteners in 1995 throughout Southeast Asia. They plan to introduce aspartame to India and to test market an aspartame tabletop sweetener in China during 1995 (Monsanto 1994).

1995

In a June 12, 1995 article which appeared in Food Chemical News, Thomas Wilcox, the FDA epidemiology branch chief was quoted as saying, "FDA has no further plans to continue to collect adverse reaction reports or monitor research periodically done on aspartame." (Food 1995)

Monsanto/NutraSweet is beginning to test market Equal in Shanghi, China. It is part of a plan to push their poison on

60 million Chinese in the coastal cities (Millman 1995).

1996

Distinguished Neuroscientist research, Dr. John W. Olney, publishes research showing that aspartame may be a brain tumor agent. He shows that aspartame caused brain cancer in preapproval research, that a breakdown product of aspartame has caused mutations in vitro, and that from 4 to 13 years after approval there was a significant increase in the conversion of less deadly brain tumors to much more deadly brain tumors (same types as seen in preapproval research) in susceptible populations (Olney 1996). Monsanto and the FDA respond with irrelevant statements regarding the overall brain tumor rate (NutraSweet 1996).

[Note: Politically/Financially motivated decisions that completely ignore public health (as seen throughout this document) are fairly common in the U.S. when it comes to food, drugs, and chemical "safety."]

References

Brannigan, Vincent, 1983. "The First FDA Board of Inquiry: The Aspartame Case," IN "Law and Science in Collaboration," edited by J.D. Nyhart and Milton M. Carrow, Lexington Books, D.C. Heath and Company, Lexington, Massachusetts, c1983, page 181-210

Buzzard, James A., 1976a. Testimony of James A. Buzzard, G.D. Searle, before the U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 2," No. Y4.L11/2:P49/2/976/pt2, CIS# S541-82, page 168.

Buzzard, James A., 1976b. Letter from James A. Buzzard of G.D. Searle to Dr. Alexander M. Schmidt, Commissioner, U.S. Food and Drug Administration, January 7, 1976, "Good Laboratory Practices" proposal enclosure, Reprinted in U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 2," No. Y4.L11/2:P49/2/976/pt2, CIS# S541-82, page 185-213.

Cloninger, M.R., R.E. Balwin 1970. "Aspartylphenylalanine methyl ester: a low calorie sweetener," Science, Volume 170, page 81.

Congressional Record 1982. "Orphan Drug Act," Congressional Record, December 14, 1982, page 30445.

Congressional Record 1985a. "Saccharin Study and Labeling Act Amendments of 1985," Congressional Record, Volume 131, No. 58, May 7, 1985, page S5489-S5519.

Congressional Record 1985b. "Aspartame Safety Act," Congressional Record, Volume 131, No. 106, August 1, 1985, page S10820-10847.

Farber, Steven A. 1989. "Aspartame and the Regulation of Food Additives: A Study of FDA Decision-Making and a Proposal for Change," Master of Science in Technology and Public Policy Thesis at Massachusetts Institute of Technology, Cambridge, MA 02139.

Federal Register 1973. Notice of Filing of Food Additive Petition, G.D.Searle & Company. Federal Register, Volume 38, page 5,921.

Federal Register 1974. Volume 39, page 27137.

Federal Register 1975. Volume 40, page 56907, December 5, 1975.

Federal Register 1979. "Ruling on Objections and Notice of Hearing Before a Public Board of Inquiry; Aspartame," Federal Register, Volume 44, page 31,717.

Federal Register 1981. "Aspartame: Commissioner's Final Decision," Federal Register, Volume 46, page 38284-38308.

Federal Register 1983. "Food Additives Permitted for Direct Addition to Food: Aspartame," 48(July 8): 31376-31382.

Federal Register 1984. "Food Additives Permitted for Direct Addition to Food for Human Consumption; Aspartame," Volume 49, No. 36, February 22, 1984, page 6672-6682.

Food 1995. "Aspartame Adverse Reaction Reports Down in 1994 From 1985 Peak: FDA," Food Chemical News, June 12, 1995, page 27.

Freeman, Martha, 1973. Memorandum from Martha A. Freeman, Supervisory Medical Officer, FDA Division of Metabolic and Endocrine Drug Products to Dr. C.J. Kokosi, FDA Division of Toxicology, September 12, 1973, Reprinted in US Senate 1987, page 326-336.

Furia, T.E. 1972. CRC Handbook of Food Additives. 2nd ed., Cleveland, Ohio: CRC Press, pp. 193.

GAO 1986. "Six Former HHS Employees' Involvement in Aspartame's Approval," United States General Accounting Office, GAO/HRD-86-109BR, July 1986.

GAO 1987. "Food Additive Approval Process Followed for Aspartame," United States General Accounting Office, GAO/HRD-87-46, June 1987.

Gordon, Gregory, 1987. "NutraSweet: Questions Swirl," UPI Investigative Report, 10/12/87. Reprinted in US Senate (1987, page 483-510).

Gordon, Gregory, 1996. "FDA resisted proposals to test aspartame," Minneapolis Star-Tribune, November 22, 1996.

Graves, Florence, 1984. "How Safe is Your Diet Soft Drink," Common Cause Magazine, July/August 1984. Reprinted in Congressional Record (1985a, pages S5497-S5506)

Griffin, G. Edward, 1974. "World Without Cancer," America Media, Westlake Village, California, ISBN 0-912986-09-3, c1974, page 395. Quote from "Autopsy On The A.M.A.," San Francisco Chronicle, January 2, 1970, page 42.

Gross, Adrian, 1975. Memorandum from Mr. Adrian Gross, Scientific Investigations Staff to Mr. Carlton Sharp, Chairman, Searle Investigation Task Force, September 29, 1975, Reprinted in U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1975, Part 1," No. Y4.L11/2:P49/2/975, CIS# S541-16, page 440+.

Gross, Adrian, 1976b. Memorandum from Mr. Adrian Gross, Scientific Investigations Staff to Mr. Carlton Sharp, Chairman, Searle Investigation Task Force, March 15, 1976, Reprinted in U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 3," No. Y4.L11/2:P49/2/976/pt.3, CIS# S541-12, page 310-376.

Gross, Adrian, 1985. Statement from Dr. Andrian Gross, Former FDA Investigator and Scientist, "Aspartame Safety Act," Congressional Record, Volume 131, No. 106, August 1, 1985, page S10835-S10840.

Gross, Adrian, 1987a. Letter from Dr. Andrian Gross, Former FDA Investigator and Scientist to Senator Howard Metzenbaum regarding pre-approval tests by G.D. Searle,

October 30, 1987, Reprinted in US Senate 1987, page 430-439.

Gross, Adrian, 1987b. Letter from Dr. Andrian Gross, Former FDA Investigator and Scientist to Senator Howard Metzenbaum regarding pre-approval tests by G.D. Searle, November 3, 1987, Reprinted in US Senate 1987, page 443-453.

Helling, Herbert, 1970. Memorandum from Herbert Helling, G.D. Searle Official to several G.D. Searle Officials, regarding Food and Drug Sweetener Strategy, December 28, 1970, Reprinted in U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 2," No. Y4.L11/2:P49/2/976/pt2, CIS# S541-82, page 16-19.

Kennedy, Edward M., 1976. Testimony of U.S. Senator Edward M. Kennedy at the U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 3," No. Y4.L11/2:P49/2/976/pt.3, CIS# S541-12.

Mazur, Robert, James Schlatter, Arthur Goldkemp 1969. "The Structure-Taste Relationship of Some Dipeptides," Journal of the Americna Chemical Society, Volume 91, No. 2, page 684.

Merrill, Richard, A., 1977. Memorandum from Richard A. Merrill, Chief Counsel, Food and Drug Administration to U.S. Attorney, Samuel K. Skinner, January 10, 1977, Reprinted in Congressional Record 1985b, page S10827-S10835.

Metzenbaum, Senator Howard, 1985. Testimony of U.S. Senator Howard Metzenbaum of Ohio at "Aspartame Safety Act," Congressional Record, Volume 131, No. 106, August 1, 1985, page S10821.

Millman, Nancy, 1995. "King of the Tabletop," Chicago Tribune, Sunday, September 17, 1995, page C1.

Monsanto 1990. "Monsanto Annual Report," 1990.

Monsanto 1991. "Monsanto Annual Report," 1991.

Monsanto 1992. "Monsanto Annual Report," 1992.

Monsanto 1993. "Monsanto Annual Report," 1993.

Monsanto 1994. "Monsanto Annual Report," 1994.

Mullarkey, Barbara, 1992. "Bittersweet Aspartame: A Diet Delusion" by Barbara Alexander Mullarkey, NutriVoice, P.O. Box 946, Oak Park, Illinois 60303, (708) 848-0116.

Mullarkey, Barbara, 1994b. Account of John Cook as published in Informed Consent Magazine. "How Safe Is Your Artificial Sweetner" by Barbara Mullarkey, September/October 1994. Available from Informed Consent Magazine, P.O. Box 935, Williston, ND 58802-0935, 701/859-3002. Available from NutriVoice, P.O. Box 946, Oak Park, Illinois 60303, (708) 848-0116.

Mullarkey, Barbara, 1995. Conversations between Mark D. Gold and Barbara Mullarkey in 1995.

NutraSweet 1996. NutraSweet Internet Web Page: http://www.nutrasweet.com/.

Olney, John W., et al., 1970. "Brain damage in infant mice following oral intake of glutamate, aspartate or cysteine," Nature, Volume 227, page 609-610.

Olney, John W. 1987. Letter from Dr. John W. Olney, Neuropathologis, Washington University School of Medicine, to Senator Howard M. Metzenbaum, December 8, 1987, Presented in the record before the U.S. Senate Committee on Labor and Human Resources, November 3, 1987 regarding "NutraSweet Health and Safety Concerns." Document # Y 4.L 11/4:S.HR6.100, page 468-476.

Olney, John W., Nuri Farber, Edward Spitznagel, Lee Robins, 1996. "Increasing Brain Tumor Rates: Is There a Link to Aspartame?" Journal of Neuropathology and Experimental Neurology, Volume 55, No. 11, Page 1115-1123.

Reynolds, W. Ann, N. Lemkey-Johnston, L.J. Filer, Jr., R.M. Pitkin, 1971. "Monosodium Glutamate: Absence of Hypothalamic Lesions After Ingestion by Newborn Primates," Science, Volume 172, page 1342-1344.

Schmidt, Alexander M., 1976b. Statement by Alexander M. Schmidt, Commissioner, U.S. Food and Drug Administration before the U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 2," No. Y4.L11/2:P49/2/976/pt2, CIS# S541-82, page 50-110.

Schmidt, Alexander M., 1976c. Statement by Alexander M. Schmidt, Commissioner, U.S. Food and Drug Administration before the U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 3," No. Y4.L11/2:P49/2/976/pt.3, CIS# S541-12, page 3-56.

Searle 1975. "G.D. Searle Annual Report," 1975.

Searle, Daniel C. 1976a. Statement of Daniel C. Searle, Chief Executive Officer, G.D. Searle & Co. before the U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 2," No. Y4.L11/2:P49/2/976/pt2, CIS# S541-82, page 173-184.

Searle, Daniel C. 1976b. Letter from Daniel C. Searle, Chief Executive Officer, G.D. Searle & Co., to U.S. Senator Edward M. Kennedy, February 13, 1976, Reprinted in U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 2," No. Y4.L11/2:P49/2/976/pt2, CIS# S541-82, page 279-311.

Sharp, Carlton, 1975. Memorandum from Carlton Sharp and Searle Investigation Task Force to the Searle Investigation Steering Committee, December 8, 1975, Reprinted in U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 2," No. Y4.L11/2:P49/2/976/pt2, CIS# S541-82, page 24-28.

Stegink, Lewis D., Filer L., 1984a. "Aspartame: Physiology and Biochemistry," Marcel Dekker, Inc., N.Y.

Stoddard, Mary Nash, 1995a. "The Deadly Deception" Compiled by the Aspartame Consumer Safety Network for volumes of available published information, ACSN, P.O. Box 780634, Dallas, Texas 75378, (800) 969-6050.

US Senate 1975. U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative

Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1975, Part 1," No. Y4.L11/2:P49/2/975, CIS# S541-16.

US Senate 1976a. U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 2," No. Y4.L11/2:P49/2/976/pt2, CIS# S541-82.

US Senate 1976b. U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary, "Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976, Part 3," No. Y4.L11/2:P49/2/976/pt.3, CIS# S541-12.

US Senate 1987. U.S. Senate Committee on Labor and Human Resources, November 3, 1987 regarding "NutraSweet Health and Safety Concerns." Document # Y 4.L 11/4:S.HR6.100.

USDA 1988. "1988 United States Department of Agriculture Situation and Outlook Report; Sugar and Sweeteners." Washington, DC: U.S. Government Printing Office, pp. 51.

Verrett, Jacqueline, 1987. Statement of Dr. Jacqueline Verrett, Former Toxicologist, U.S. Food and Drug Administration before U.S. Senate Committee on Labor and Human Resources, November 3, 1987 regarding "NutraSweet Health and Safety Concerns." Document # Y 4.L 11/4:S.HR6.100, page 383-390.

Wilson, Steve, 1985. "Sweet Suspicions," Television broadcast and interviews regarding aspartame. Transcript in Congressional Record (1985b, page S10826-S10827)