Journal of Environmental Science and Health

Part A
Environmental Science
and
Engineering
including
Toxic and Hazardous Substances Control

Part B
Pesticides, Food Contaminants
and
Agricultural Waste

Part C
Environmental Carcinogenesis Reviews

Journal of Environmental Science and Health
Part A
ENVIRONMENTAL SCIENCE AND ENGINEERING
Including Toxic and Hazardous Substances Control

Part B
PESTICIDES, FOOD CONTAMINANTS,
AND AGRICULTURAL WASTES

Part C
ENVIRONMENTAL CARCINOGENESIS REVIEWS

J. ENVIRON. SCI. HEALTH, A20(8), 863-901 (1985)

ASPARTAME-- A NEW FOOD INGREDIENT

REPLY TO THE CRITICAL COMMENTS OF WOODROW C. MONTE*

Key Words: Aspartame, L-phenylalanine, L-aspartic acid, methanol

Frank M. Sturtevant, Ph.D.

Office of Scientific Affairs
Research and Development Division
G.D. Searle & Co., 4901 Searle Parkway,
Skokie, IL 60077

ABSTRACT

Aspartame, a recently marketed dipeptide sweetening agent, was discovered accidentally in 1965. Following extensive research and development, the product was approved for various uses by the FDA in 1974, 1981 and 1983. Aspartame has not been without its critics, however. W.C. Monte of Arizona has repeatedly criticized aspartame on

* From a presentation at the National Environmental Health Association's 1984 Annual Educational Conference, Grand Rapids, Michigan, June 26, 1984

 0360-1226/85/2008-0863$3.50/0

television and in filings with regulatory agencies and the courts, who have uniformly rejected his arguments. In a recent publication in a journal for which he serves as an editor, Monte ignored scientific evidence to the contrary and raised questions about the safety of aspartame. The allegations were directed towards the three metabolic products L-phenylalanine, L-aspartic acid, and, particularly, methanol. Responses to Monte's various principal charges are presented. In addition, Monte recounted the death of a plant worker exposed to aspartame, implying that death had been caused by aspartame-derived methanol. This misrepresentation of the records is corrected by a full discussion herein of their contents. It is concluded that there is overwhelming scientific evidence showing aspartame to be safe for human use, Monte's charges notwithstanding.

HISTORY OF ASPARTAME

Aspartame, the newly marketed sweetening agent, was discovered in 1965 by Searle scientist James M. Schlatter. He was working with amino acids when he discovered that one dipeptide had an intensely sweet taste similar to that of sugar. Subsequent

studies showed that this dipeptide, aspartame, was metabolized to its constituent amino acids, phenylalanine and aspartic acid, and to methanol. A battery of laboratory studies was conducted for mutagenicity, teratogenicity, carcinogenicity and chronic toxicity. A food additive petition was filed with the Food and Drug Administration (FDA) in 1973.

Aspartame was approved by the FDA in 1974. Objections were filed by Dr. John Olney of St. Louis, claiming that the aspartic acid moiety of aspartame could cause brain lesions and neuro-endocrine disorders. Attorney James Turner, a current associate of Dr. Monte, objected at the time that the phenylalanine moiety could lead to mental retardation. Although the FDA refused to stay the approval of aspartame on safety considerations, they did grant a hearing in the form of a Public Board of Inquiry.

Before the hearing could be held, however, certain questions were raised about the validity of Searle's laboratory data. As a result, some 15 aspartame studies were selected to be audited. The FDA audited three. The Universities Associated for Research and Education in Pathology (UAREP), an

outside non-profit group of university pathologists recommended by the FDA, reviewed the other 12 under contract with Searle. The experimental data in these studies were found to be authentic by UAREP and FDA. In the interim, Dr. Olney also objected to the approval on the basis that the experimental data suggested that aspartame might cause brain tumors in rats.

In January, 1980, a Public Board of Inquiry, composed of three independent scientists, met to hold a hearing and to review the data[30]. The Board's decision, issued in October, 1980, found that aspartame did not pose a risk of brain lesions, mental retardation, or neuro-endocrine disorders. The Board also found that the available data did not rule out the possibility of brain tumors in rats. They suggested that Searle conduct another study in rats at doses closer to anticipated human doses rather than at immense multiples thereof. In July, 1981, following an appeal, the FDA Commissioner issued his decision. He agreed with the Board that aspartame did not pose a risk of mental retardation, brain lesions, or neuro-endocrine disorders. He also found the Board erred in its analysis of two carcinogenicity

studies in rats that had been submitted by Searle. Both were found by the Commissioner to be negative. Searle also had submitted a recently completed third study in rats done by the Ajinomoto Company that was also negative. As a result, the Commissioner approved aspartame for "dry" uses, as initially requested by Searle and as recommended by the FDA's Bureau of Foods.

In approving aspartame, the Commissioner stated, "few compounds have withstood such detailed testing and repeated close scrutiny" (46 F.R. 38289, 7/24/81).

In September, 1982, Searle filed a petition for use of aspartame in carbonated beverages. Prior to approval in July, 1983, the FDA received comments relating to (a) the alleged ability of high doses of aspartame following fasting and carbohydrate intake to possibly affect behavior; (b) concerns relating to the methanol degradation product; and (c) the stability of aspartame in beverages. In his approval dated July 8, 1983, the Commissioner addressed each of these issues as well as reviewed the prior data once again. It is noteworthy that the Commissioner stated with regard to methanol, Dr. Monte's primary concern, "The agency finds no

cause for concern from the levels of dietary methanol resulting from the highest projected levels of aspartame consumption" (48 F.R. 31380, 7/8/83).

Following the approval, Dr. Monte formally objected, claiming that methanol did pose a risk. Mr. Turner, once again, objected and raised anew all prior objections. Both parties requested a stay and a hearing. In November, 1983, the FDA denied the stay and in February, 1984, they refused to grant a hearing. The FDA, based upon the submissions of Messrs. Monte and Turner, found that there were no new issues of fact, only allegations.

In the meantime, Messrs. Monte and Turner had petitioned the federal courts for relief, seeking an injunction against sale of aspartame and requesting a hearing. This lawsuit was dismissed by the court.

Both Dr. Monte and Mr. Turner have appealed to the U.S. Court of Appeals for the District of Columbia.

Dr. Monte, in November, 1983, also filed a petition with the State of Arizona claiming that the methanol moiety of aspartame posed a risk to Arizona consumers. This was denied by the Arizona

Department of Health Services in a detailed, 23-page decision on March 7, 1984. A re-filing in Arizona by Dr. Monte was again rejected on August 24, 1984. One month later, he responded by filing a Special Action Complaint, which is pending at the time of this writing.

The simple fact is Dr. Monte's arguments have been heard repeatedly and emphatically rejected by the FDA and the Arizona Department of Health Services. Regulatory authorities around the world, including the World Health Organization (W.H.O.), have reviewed the data supporting the safety of aspartame and have affirmed that aspartame is safe for use. Today, aspartame is approved for sale in some 40 countries.

What do the data show?

1. Metabolism studies have shown that aspartame is metabolized initially to phenylalanine and aspartic acid, two naturally occurring amino acids, and methanol[28].

2. Some 51 studies for teratogenicity, mutagenicity and carcinogenicity have been conducted and reported in the Food Additive Petition. They were uniformly negative.

In one carcinogenicity study in rats, the dose reached 6-8000 mg/kg body weight per day, for a period of 2 years (see ref. 12).

3. Studies in human beings, at aspartame doses of up to 200 mg/kg body weight in single doses, have shown that the blood levels of none of the by-products reached a toxic level[28]. (200 mg/kg is approximately 6 times the 99th percentile of anticipated daily consumption.) Further, repeated doses of 10 mg/kg every two hours do not lead to significant accumulation of phenylalanine in the plasma[28].

Notwithstanding data such as these, Dr. Monte has continued to persist in his objections, which have now expanded beyond methanol to encompass the phenylalanine and aspartic acid moieties. What does he say? I have not chosen to examine his various statements made in press conferences or to the mass media. Rather, I have looked to his only published paper on aspartame-- not a paper based on his own research, as he has published none-- but based on his selective review of the literature. It was published in the Spring, 1984, issue of <u>The</u>

Journal of Applied Nutrition[19], a non-refereed* journal of which Dr. Monte is listed as a member of the editorial board. In my review of his paper, I have found innumerable miscitations and apparent intentional misrepresentations of the literature, all of which were compounded by the apparent deliberate decision to ignore the weight of credible scientific evidence to the contrary.

Space precludes the listing of each of these errors. Therefore, I have restricted my comments to a half-dozen of the more blatant ones.

Dr. Monte does recognize that the digestion of aspartame yields phenylalanine, aspartic acid, and methanol. In his article, he addresses each of these with regard to the question of safety, with major emphasis on the subject of methanol. Each of these will be examined in turn.

PHENYLALANINE

Dr. Monte alleges[19] that Dr. Wurtman of the Massachusetts Institute of Technology "presented data to the FDA demonstrating that in humans the

---

* personal communication from the Editor-in-Chief

feeding of a carbohydrate with aspartame significantly enhances aspartame's positive effect on plasma and brain phenylalanine and tyrosine levels (48 Federal Register at 31379)." The Federal Register reference does not support Dr. Monte's assertion. This reference states that "limited details" on five human subjects were provided in whom an increased ratio of plasma phenylalanine to other neutral amino acids was observed following 1000 mg aspartame plus 200 gm sugar in the fasting state. Nothing whatsoever was said about human brain phenylalanine and tyrosine levels. In fact, it would require human brain biopsies to show these. On reviewing Dr. Wurtman's letters to the FDA, one finds no mention of any behavioral signs. The FDA concluded, "It's difficult, however, if not impossible, to interpret the significance of the experiments" in this uncontrolled study. The suggested changes in neurotransmitter function were deemed by the FDA to be "unwarranted extrapolations."

Dr. Monte further states[19] that there are "sound scientific reasons" to believe that increased brain levels could affect bodily functions such as blood pressure, for which he

carelessly cited the wrong letter by Wurtman[38]. Another letter published three months later[16] did report a fall in blood pressure, measured indirectly, of rats injected intraperitoneally (not orally) with 200 mg of aspartame per kg. This is contrary to the findings of experimental observations at Searle on hypertensive animals (unpublished data).

ASPARTIC ACID

Dr. Monte asserts[19] that, with regard to aspartic acid, "under conditions of excess absorption it has caused endocrine disorders in mammals with markedly elevated plasma levels of luteinizing hormone and testosterone in the rat...", with Stegink[29] cited as authority. This reference is not at all germane to the subject. He should have cited Olney[21]. But even this was not an experiment involving absorption of aspartic acid from the gastrointestinal tract, as Dr. Monte implies. Rather, it involved the subcutaneous injection of 1000 mg of the test substance per kg. Contrary to the unfounded assertion of Dr. Monte, this substance was glutamic acid, not aspartic acid.

Dr. Monte then asserted that aspartic acid caused "release of pituitary gonadotropin and prolactin in the rhesus monkey," citing Wilson and Knobil[36]. In examining this authority of Monte's, we see that the paper cited has nothing to do with aspartic acid. The reported experiment actually involved the administration of 15 mg of N-methyl-D,L-aspartate per kg to four monkeys. As I pointed out in my testimony before the Public Board of Inquiry, studies on synthetic compounds such as N-methyl-D,L-aspartate are not relevant to aspartame, as they "do not arise from the metabolism of aspartame, nor have they been shown to be handled by the body in the same manner as aspartate"[31]. Further, the experiment involved <u>intravenous</u> injection of the compound, not oral absorption as Dr. Monte implies.

Thus, we see that Dr. Monte has managed to commit five errors with two references in a single sentence. For one article, he had the wrong reference; for both articles, he had the wrong compounds and the wrong routes of administration. These published data were rejected by the Public Board of Inquiry and by the FDA Commissioner in their review of the scientific evidence relating to the safety of aspartame.

METHANOL

In his many public pronouncements, Dr. Monte has several recurring major themes. These all deal with alleged issues of safety concerning the methanol degradation product, which represents 10% by weight of aspartame. They have all been reviewed and re-reviewed by the FDA and other health authorities. Dr. Monte's allegations have been uniformly rejected. What are his major themes?

1. Dr. Monte asserts that methanol is a "cumulative poison." Over 400 years ago, Paracelsus (1493-1541) noted, "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy"[8]. Frequency of administration and dose together determine whether a substance accumulates in the body. As the Arizona Department of Health instructed Dr. Monte in denying his petition to them (3/7/84), "Reference to methanol as a 'cumulative poison' is misleading. That term must be examined in the context of dose level and frequency." Indeed, to do otherwise is to ignore the conversion of methanol to formaldehyde and

then to formate, which is, after all, the actual toxic by-product of methanol. As will be shown, no conceivable dietary use of aspartame can lead to the accumulation of methanol or formate. Methanol from dietary aspartame use cannot be a "cumulative poison."

2. The methyl alcohol syndrome, Dr. Monte asserts[19], is produced consistently "only in humans and no other test animal, including monkeys." The authorities for this position are given as Roe[23] and Tephly et al.[34]. Roe has published little original experimental work on methanol in recent years. Since Monte accepts the work of Tephly*, a recognized authority on methanol, it is appropriate to review not only his 1974 article[34], which Dr. Monte cites, but also Tephly's most recently published, 1984 review[33], which he ignores. This review incorporates research results appearing in

---

* Both Monte (9/21/84) and Turner (8/31/84) have publicly averred that the methanol work of Tephly et al.[26] had been severely criticized by Smith and Taylor[26]. This is a gross mischaracterization of the latter article.

the 10-year interim. Following the 1974 article, a series of papers was published by Tephly and others documenting the ocular toxicity of methanol in monkeys. With methanol protocol designed to produce metabolic acidosis with accumulation of blood formic acid[18], these workers observed optic disc edema[10] and, microscopically, retinal ganglion cell degeneration[3]. Most significantly, the results are similar to those produced by administration of formate in monkeys[17]. Contrary to Dr. Monte's position, Tephly and McMartin, in their 1984 review[33], hold that the monkey <u>is</u> a model for methanol poisoning in man, and that "a syndrome similar to that described for humans" has been produced. The best that can be said for Dr. Monte is that he has been selective in his use of the scientific literature. Experiments in monkeys have clearly documented that ocular toxicity can be produced by the administration of methanol or formate, the toxic metabolite. Experimentally, adverse effects have <u>not</u> been seen in monkeys

receiving up to 3,000 mg aspartame/kg/day for 9 months[22].

3. An often repeated charge by Dr. Monte is that "Formaldehyde is a known carcinogen"[19]. For this he cites the Third Annual Report on Carcinogens[35], which is merely a list compiled by the National Toxicology Program. Two lists are provided. List "a" consists of substances "that are known to be carcinogenic." Formaldehyde is not so listed. List "b" consists of substances "that may be reasonably anticipated to be carcinogens". Formaldehyde does appear here, with a reference to p.158, where the text states, "A significant incidence of squamous-cell carcinomas of the nasal cavity was induced in both strains of rats but not mice" subjected to inhalation exposure. The reference footnote is the same as Monte's reference to an IARC monograph[11]. This last publication characterizes other inhalation studies in mice and hamsters and one subcutaneous administration study in rats as "inadequate for evaluation". "Three epidemiological

studies of people exposed to formaldehyde have been published"; the IARC classifies this evidence for carcinogenicity in humans as "inadequate"[11].

Thus, when Dr. Monte denotes formaldehyde as a "known carcinogen," this is true only in the case of inhalation studies in rats and mice resulting in squamous cell carcinomas of the nasal cavity[1,14]. Carcinogenicity "has not been shown for ingested formaldehyde at any level" according to the FDA in a "Talk Paper," 1/20/84. Dr. Monte never explains this in his public media charges (see, e.g., "LA Today," KABC-TV, Los Angeles, 4/16/84). The final word, then, is that formaldehyde should not be characterized as a known general carcinogen, as implied by the term "known carcinogen."

In an attempt to buttress arguments relating to formaldehyde, Dr. Monte has stated that a condensation product of formaldehyde and glycerin may be formed in vivo. The product, glycerol formal, he asserts, "is a potent teratogen causing an

extremely high incidence of birth defects in laboratory animals," citing Stegink's human studies on blood methanol[29]. Stegink makes no such statement. One may assume that Monte intended to cite Staples' book chapter entitled "Teratogenicity of Formaldehyde"[27]. Does this reference support Monte's claim? First, Staples reviews the literature on the teratogenicity of formaldehyde and concludes, "formaldehyde has not been demonstrated to be teratogenic in any species to date." Second, Staples cites the papers of an Italian group to the following effect: "glycerol formal, a commonly used solvent for toxicity testing at least in Italy, was reported to be teratogenic after administration subcutaneously or intramuscularly to the rat" (emphasis supplied). "It is not known whether humans are likely to be exposed to this condensation product or whether the product can be formed in vivo; therefore, its significance as a hazard to the human conceptus is unknown". In spite of the

fact that Staples says in vivo formation is unknown, Monte cites this reference for his parenthetical claim "which may be formed in vivo"[19]. This then was the sole basis for Dr. Monte's televised public warnings not to consume aspartame during pregnancy ("LA Today;" "Open House," loc. cit.), which completely ignore the battery of studies in the record on the safety of aspartame in pregnancy. These studies have been reviewed by governmental authorities around the world, including Canada, Japan, the United Kingdom, W.H.O., who have approved aspartame; not a single one contraindicates the use of aspartame in pregnancy. The food additive petition for aspartame includes no less than 51 studies on mutagenicity, teratogenicity and carcinogenicity. In short, Dr. Monte's warnings concerning aspartame in pregnancy are unfounded.*

---

* In a recent talk in Flagstaff, Arizona (9/21/84), Dr. Monte presented preliminary data purporting to show decreased implantation sites in rats administered methanol during pregnancy. He stated that the teratogenicity of methanol itself had never been tested, which is incorrect[20,24,39].

4. Another of Dr. Monte's themes claims that methanol occurs in natural food sources, but ethanol occurring simultaneously serves as a protectant, while this is not the case for methanol derived from aspartame. It is not contested that ethanol does decrease the rate of conversion of methanol to its toxic products. What Dr. Monte ignores here is the fact, admitted elsewhere by him in the same paper[19], that ethanol is metabolized 5-7 times faster than methanol, so that after the ethanol is rapidly depleted, methanol still persists. The disappearance rates are zero-order, as Monte claims, only above certain elevated blood levels, and circadian variation in rates[32] is not addressed by him at all. The rate-order for methanol has been shown to be dependent upon blood level[33]. These considerations are basic to the understanding of the competitive pharmacokinetics of the alcohols. Thus, ethanol could serve as a protectant only if its blood level is maintained above critical levels. It can be estimated by pharmacokinetic

calculations that such a protectant action of the ethanol present in 500 ml orange juice, for example, persists for less than one minute after a simultaneous aspartame dose of 200 mg/kg.

Equally important, Dr. Monte ignores the fact that blood methanol levels following single doses (in 500 ml orange juice) of 200 mg aspartame per kg do not create a blood methanol or formate level known to be toxic[29]. In fact, the severity of methanol toxicity does not relate to the blood level of methanol, but to that of formate[33]. Thus, the replies to Dr. Monte's charges are: (a) any protectant effect of ethanol in foods is evanescent, and (b) there is no elevation in blood methanol following excessive aspartame doses to have warranted any protection in the first place.

5. Dr. Monte asserts[19] that the Environmental Protection Agency (EPA) "recommends a minimum acute toxicity concentration of methanol in drinking water of 3.9 parts per million, with a recommended limit of consumption below 7.8

mg/day." He cites as authority the Multimedia Environmental Goals for Environmental Assessment (MEG)[7]. Monte's characterization of these MEGs as recommendations of the EPA is simply wrong. The situation is clearly described in the chapter on "Exposure Limits" in Monte's reference of Wimer et al.[37], which he does not cite in the present context. The MEGs were developed by the Research Triangle Institute, a private firm, under contract with the EPA, to facilitate evaluation of chemical pollutants. The MEGs for methanol were derived solely on the basis of a Threshold Limit Value for methanol calculated by the American Conference of Governmental Industrial Hygienists. The Threshold Limit Value for methanol is a recommendation by the Hygienists of the level of airborne methanol to which workers may be repeatedly exposed day after day without adverse effect[2]. The Hygienists' publication provides, [These limits] "are not intended for use, or for modification for use, as a relative index of hazard or

toxicity..."[2]. The Research Triangle Institute used the Threshold Limit Values for airborne methanol to construct an MEG for methanol in ambient water. To attempt to equate this with an EPA recommended daily limit of consumption is absurd. Nevertheless, Dr. Monte states the EPA recommended such a consumption limit of 7.8 mg/day for methanol. The absurdity of Dr. Monte's position is exemplified by comparing the MEG for acetic acid of 0.345 mg/l with the FDA food tolerance level generally recognized as safe in the Code of Federal Regulations (21 CFR 184.1005) of some 1500 mg/l, which is more than 4,000 times greater than the MEG. Would Dr. Monte ban salad dressings on this basis?

6. Dr. Monte gives the lethal dose of methanol as 10 ml, citing Gosselin[9] as the source. When one refers to that source, one finds the statement that 10 ml are toxic; that the fatal dose is between 60 and 240 ml. Monte's own reference of Roe[23] gives 1000 mg/kg as a suggested minimal lethal dose, the actual figure not having

been determined. For a 50-kg person, this is about 62 ml. Thus, these two references of Monte suggest about 60 ml as the minimal lethal dose, but he chooses to misquote a figure one-sixth that amount. To reach the so-called toxic dose of 10 ml would require the instantaneous consumption of over 400 12-oz cans of soda fully sweetened with aspartame. To reach the fatal dose would require the instantaneous consumption of 2,400 to 9,600 cans! For colas containing a blend of aspartame and saccharin, the figures are 12,000-48,000 cans.

7. Anecdotal reports from aspartame users are employed by Dr. Monte in such a fashion as to suggest that the symptoms complained of are those of methanol poisoning*.

Dr. Monte claims that methanol exposure "often" produces complaints of multiple neuritis with shooting pains in the extremities. He obtains this from two cases published in 1905, which the original

---

* This hypothesis is not confirmed by an analysis of consumer complaints by the Centers for Disease Control (FDA Talk Paper, 11/1/84; Morbid. Mortal. Weekly Rep. 33:605-607, 1984).

author described as "slight" in severity and occurring only in the upper extremities[13]. Two cases reported 79 years ago do not warrant the adverb "often."

If, in Dr. Monte's experience[19], symptoms of peripheral neuropathy are "not an uncommon anecdotal consumer complaint following long-term consumption of aspartame," it is suggested he look elsewhere for the cause. Chronic alcoholism or vitamin B_1 deficiency might be good places to begin. Aspartame is not. Consider the amount of blood methanol provided by the aspartame molecule: a dose of 34 mg of aspartame per kg, which represents the 99th percentile of projected daily use (49F.R. 6676, 2/22/84), would yield 3.4 mg of methanol per kg, which does not result in a detectable blood level[29]. Formate is the toxic product of methanol in primates[29] and the former is not increased in the blood after an aspartame dose of 200 mg/kg in human beings[29]. Taking the maximal concentration of available methanol from a beverage fully sweetened with

aspartame to be 56 mg/l (48 F.R. 31380, 7/8/83), we can equate the aspartame dose of 200 mg/kg to represent a methanol dose of 20 mg/kg times a 50-kg person, or 1000 mg of methanol. Dividing this by 56 mg/l gives 17.9 liters of beverage. Dividing this by 354 ml beverage per 12-oz can gives 50.6 cans. What this means is that the instantaneous consumption and metabolism of over 50 cans of aspartame-sweetened diet beverage would not yield a detectable increase in blood formate! In brief, there is no feasible way to drink enough aspartame to implicate it in signs of peripheral neuropathy. Dr. Monte's interpretations of anecdotal consumer complaints are either misleading him or are being used by him to mislead his audience.

A Case Report

Probably the most egregious example of Dr. Monte's mishandling of anecdotal reports involves the unfortunate death, at home, of a former employee in Searle's manufacturing plant in Phoenix.

Dr. Monte[19] recounts this case report as follows:

> "A 21-year old non-drinking male who had been exposed daily to the fine dust of aspartame at the packaging plant he had worked for over a year, was complaining of blurred vision, headaches, dizziness, and severe depression before his sudden death. An autopsy revealed (aside from the organ involvement one might expect from methanol toxicity) myocardial hypertrophy and dilatation with the myocardiopathy and left ventricle involvement reminiscent of alcoholic cardiomyopathy. Alcoholic cardiomyopathy however typically occurs in 30-55 year old men who have a history of alcohol intake in quantities comprising 30 to 50 percent of their daily caloric requirement over a 10 to 15 year period[56]."

Aside from the fact that Monte's reference 56 to an H.S.S. Report to Congress does <u>not</u> support his final statement*, it is necessary to make a

---

* Monte's final sentence was actually copied verbatim from Segel et al.[25], who in turn cite another source, which does not support the statement. The latter article merely cites findings in yet another paper[6]. This is a concatenation of erroneous citations.

point-by-point refutation of the false representations and omissions being made by Dr. Monte in describing this case, because this is the first time they have appeared in print. Dr. Monte is implying that aspartame inhalation led to blood methanol levels that caused heart damage consistent with that found in chronic alcoholics although the employee himself was a non-drinker. His suggestions are without factual foundation.

The medical and personnel records reveal the following:

> The subject had <u>not</u> been exposed daily to aspartame for over a year. He was hired as a material handler in the aspartame area on 3/22/82. Beginning 10/5/82, he went on short-term disability because of dilated cardiomyopathy and ventricular ectopy, possibly subsequent to unrecognized viral myocarditis, and for which he was placed on the drug quinidine. He returned to work on 12/6/82. Following his job reassignment on 1/24/83 to the time of his death 3/31/84-- a period of over 14 months-- he was <u>not</u> exposed daily to aspartame. In fact, during the 10 months before his

death, he was studying data processing off-plant at the Miller Institute (6/8/83-3/19/84) and then later working in the data processing unit at the plant (3/19/84-3/31/84).

There is nothing at all in the autopsy report concerning "organ involvement one might expect from methanol toxicity." (From his immediately preceding paragraphs, it would appear that Dr. Monte is making reference here to pancreatitis, which the decedent did not have.)

There was cardiomyopathy including myocardial hypertrophy and dilatation [i.e., an enlarged heart weighing 540 gm]; however, this was consistent with his history of (a) ventricular fibrillation and cardiopulmonary arrest on 10/1/82, (b) left ventricular dilatation, and (c) continuing premature ventricular contractions.

Next, the autopsy report does not liken the subject's heart problem, or cardiomyopathy, to that seen in alcoholism. The Merck Manual[4], frequently used by Dr. Monte as a medical authority, describes

this heart condition as "cardiomegaly and congestive heart failure," which may be accompanied by vitamin B_1 deficiency heart disease. Aside from the non-specific condition of an enlarged heart, there is nothing in the autopsy report "reminiscent" of alcoholic cardiomyopathy.

Finally, there was no quinidine found in the subject's blood at autopsy, suggesting he died of cardio-pulmonary arrest after having discontinued the quinidine, possibly because of the side effects of which he had complained (see below).

In his description of the case, Dr. Monte fails to reveal the following relevant facts:

- The subject had been taking quinidine for ventricular ectopic activity.
- Blurred vision, headaches, and dizziness are known side effects of quinidine, according to the official prescribing information, as well as Goodman & Gilman's textbook[8].
- His depression had been attributed to a history of anoxic encephalopathy (i.e., brain damage due to oxygen deprivation when

his heart stopped and he received CPR on 10/1/82).

Finally, Dr. Monte makes the blatant misrepresentation that the subject was a non-drinker. This would have the effect of (a) removing any "protective" action of ethanol from consideration, and (b) deleting any possible direct effect of drinking on what Dr. Monte called "involvement reminiscent of alcoholic cardiomyopathy." The truth of the matter, according to the medical records, is that the subject consumed alcohol in moderate amounts.

Incidentally, it is worth considering that the subject had a heart problem noted on his pre-employment physical exam.

It should be apparent that Dr. Monte, a layman in this area, has extracted selectively from the records those items serving to make his case that this employee died of methanol poisoning after working with aspartame. As elsewhere, he has continued reckless misrepresentation of the records or fabricated their contents. A full review of the medical, autopsy, and personnel records has led Searle's medical staff to the conclusion that there

is no rational basis at all for Dr. Monte's suggestion.*

CONCLUSIONS

I have attempted in this brief article to review the major charges Dr. Monte has leveled at the safety of aspartame. I have endeavored to respond by pointing out the grossest errors he commits in making these accusations. In this regard, I have recalled relevant scientific information, including the following major points:

1. Aspartame yields methanol, 10% by weight.
2. Acute and chronic studies in animals have addressed the question of mutagenicity, carcinogenicity, and teratogenicity of aspartame and its breakdown products, including methanol. Doses of aspartame in rats reached to 6-8000 mg/kg/day for 2 years. The results were negative.

---

* The evaluation of this case by the Centers for Disease Control stated that the subject was a heavy smoker and an occasional heavy drinker. It concluded, "Evidence that exposure to aspartame caused or aggravated his symptoms or his heart disease could not be established by interview with physicians in attendance, with the medical examiner, or from review of case records." (See addendum.)

3. In infant primates, aspartame up to 3000 mg/kg/day for 9 months did not produce behavioral changes or signs of toxicity.

4. Single oral doses of aspartame in man up to 200 mg/kg did not elevate blood formate levels. Blood methanol levels were well below any known toxic levels.

Based upon extensive review of all of the data in the voluminous Administrative Record for aspartame, the FDA stated that "the agency finds no cause for concern from the levels of dietary methanol resulting from the highest projected levels of aspartame consumption."

Further, FDA Commissioner Hayes has stated, "few compounds have withstood such detailed testing and repeated close scrutiny." The verdict has been rendered repeatedly: aspartame is safe.

ADDENDUM

The case report described above was included in the "Evaluation of Consumer Complaints Related to Aspartame Use" by the Centers for Disease Control (unpublished, 11/1/84, pp. 144-145). Because of the seriousness of Dr. Monte's allegations and misrepresentations concerning this case[19], and his

continuing reference to it (Flagstaff, AZ, 9/21/84), the verbatim report of the CDC is given below.

> This is a complicated case of a 21-year-old white male worker in an aspartame production facility who died of acute myocardial failure. It was reported by his stepfather; and interviews were conducted with the mother, wife, stepfather, and physicians of the deceased, as well as with the medical examiner who performed the postmortem examination.
>
> The case subject was an apparently healthy heavy smoker and occasionally heavy user of alcoholic beverages who developed in August 1981 severe right-sided chest pain for which he was hospitalized. No definitive diagnosis was made; however, it appeared from an EKG taken at the time that he had some preexisting heart disease with a contraction defect (junctional PVC, LVH by voltage criteria, bradycardia, and relatively increased QT and decreased PR intervals.) Subsequently, he began working with aspartame in large amounts and consumed aspartame-containing products. He intermittently had chest pains, dizzyness, blurred vision, and hot flashes; in October of 1982, he collapsed at home with cardiac arrest associated with ventricular fibrillation. He developed a transient anoxic encephalopathy and was found to have a dilated cardiomyopathy with chronic ventricular ectopic activity and an anomalous origin of the left circumflex artery. He was followed medically and maintained on quinidine sulfate. In May of 1983, he was involved in an industrial accident, which resulted in the loss of his left arm. He was reported to then have developed intermittent chest pains, memory loss, and the onset of migraine

headaches and muscular-skeletal pains. He died in March 1984 while sleeping. Post-mortem examination diagnosed myocardial hypertrophy and dilatation, congenital anomaly of the left interior descending artery, and a myocardiopathy possibly related to viral endocarditis. Evidence that exposure to aspartame caused or aggravated his symptoms or his heart disease could not be established by interview with physicians in attendance, with the medical examiner, or from review of case records.

REFERENCES

1. Albert RE., Sellakumar AR., Laskin S., Kuschner M., Nelson N., Snyder CA. Gaseous formaldehyde and hydrogen chloride induction of nasal cancer in the rat. J. Natl. Cancer Inst. 1982; 68: 597-603.

2. American Conference of Governmental Industrial Hygienists. TLVs Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1981. Cincinnati, Ohio: ACGIH Publications Office, 1981.

3. Baumbach GL., Cancilla PA., Martin-Amat G., Tephly TR., McMartin KE., Makar AB., Hayreh MS. Methyl alcohol poisoning IV. Alterations of the morphological findings of the retina and the optic nerve. Arch. Ophthalmol. 1977; 95: 1859-1865.

4. Berkow R. The Merck Manual of Diagnosis and Therapy, 14th ed. Rahway, N.J.: Merck & Co., Inc., 1982: 1416.

5. Brigden W., Robinson J. Alcoholic heart disease. Brit. Med. J. 1964; 2: 1283-1289.

6. Burch GE., Walsh JJ., Black WC. Value of prolonged bed rest in management of cardiomegaly. J. Amer. Med. Assoc. 1963; 183: 81-87.

7. Cleland JG., Kingsbury GL. Multimedia Goals for Environmental Assessment, EPA-600/7-77-136b, E-28. Washington, D.C.: U.S. Environmental Protection Agency, 1977.

8. Gilman AG., Goodman LS., Gilman A. Goodman and Gilman's Pharmacological Basis of Therapeutics, 6th ed. New York, NY: Macmillan Publishing Co., Inc., 1980: 1603.

9. Gosselin RE. Clinical Toxicology of Commercial Products, 4th ed. Baltimore, Md.: Williams & Wilkins, 1981.

10. Hayreh MS., Hayreh SS., Baumbach GL., Cancilla P., Martin-Amat G., Tephly TR., McMartin KE., Makar AB. Methyl alcohol poisoning III. Ocular toxicity. Arch. Ophthalmol. 1977; 95: 1851-1858.

11. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 4. Lyon, France: IARC, 1982.

12. Ishii H. Chronic feeding studies with aspartame and its diketopiperazine. In: Stegink LD., Filer LJ. Jr. eds. Aspartame Physiology and Biochemistry. New York, NY: Marcel Dekker 1984: 307-319.

13. Jelliffe SE. Multiple neuritis in wood alcohol poisoning. Med. News 1905; 86: 387-390.

14. Kerns WD., Pavkov KL., Donofrio, DJ., Gralla EJ., Swenberg JA. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. Cancer Res. 1983; 43: 4382-4392.

15. Kirchner JG., Miller JM., Rice RG., Keller GJ., Fox MM. Volatile water-soluble constitutents of grapefruit juice. J. Agric. Food Chem. 1953; 1: 510-512.

16. Maher TJ., Wurtman RJ. High doses of aspartame reduce blood pressure in spontaneously hypertensive rats. New Engl. J. Med. 1983; 309: 1125.

17. Martin-Amat G., McMartin KE., Hayreh SS., Hayreh MS., Tephly TR. Methanol poisoning: Ocular toxicity produced by formate. Toxicol. Appl. Pharmacol. 1978; 45: 201-208.

18. Martin-Amat G., Tephly TR., McMartin KE., Makar AB., Hayreh MS., Hayreh SS, Baumbach G., Cancilla P. Methyl alcohol poisoning II. Development of a model for ocular toxicity in methyl alcohol poisoning using the Rhesus monkey. Arch. Ophthalmol. 1977; 95: 1847-1850.

19. Monte WC. Aspartame: Methanol and the public health. J. Appl. Nutr. 1984; 36: 42-54.

20. Nelson BK., Brightwell WS., MacKenzie DR., Burg JR., Weigel WW., Goad PT. The teratogenic effects of methanol administered by inhalation to rats. Teratology 1984; 29: 48A.

21. Olney JW., Cicero TJ., Meyer ER., de Gubareff T. Acute glutamate-induced elevations in serum testosterone and luteinizing hormone. Brain Res. 1976; 112: 420-424.

22. Reynolds WA., Bauman AF., Stegink LD., Filer LJ. Jr., Naidu S. Developmental assessment of infant macaques receiving dietary aspartame or phenylalanine. In: Stegink LD., Filer LJ. Jr. eds. Aspartame Physiology and Biochemistry. New York, NY: Marcel Dekker 1984: 405-423.

23. Roe O. Species differences in methanol poisoning. CRC Critical Rev. in Toxicol. 1982; 10: 275-286.

24. Russell LB., Montgomery CS. Use of the mouse spot test to investigate the mutagenic potential of triclosan (Irgasan® DP300). Mutation Res. 1980; 79: 7-12.

25. Segel LD., Klauser SC., Gnadt JTH., Amsterdam EA. Alcohol and the heart. Med. Clin. N. Amer. 1984; 68: 147-161.

26. Smith EN., Taylor RT. Acute toxicity of methanol in the folate-deficient acatalasemic mouse. Toxicology 1982; 25: 271-287.

27. Staples RE. Teratogenicity of formaldehyde. In: Gibson JE. ed. Formaldehyde Toxicity. Washington DC: Hemisphere Publishing Co., 1983: 51-59.

28. Stegink LD. Aspartame metabolism in humans: acute dosing studies. In: Stegink LD., Filer LJ. Jr. eds. Aspartame Physiology and Biochemistry. New York, NY: Marcel Dekker 1984: 509-553.

29. Stegink LD., Brummel MC, McMartin K., Martin-Amat G., Filer LJ. Jr., Baker GL., Tephly TR. Blood methanol concentrations in normal adult subjects administered abuse doses of aspartame. J. Toxicol. Environ. Hlth. 1981; 7: 281-290.

30. Sturtevant FM. Aspartame, a new sweetening agent. Toxicological questions discussed at a scientific hearing. Trends in Pharmacol. Sci. 1980; 1(8): X-XI.

31. Sturtevant FM. Posssible hormonal efects of aspartame ingestion. In: Stegink LD., Filer LJ. Jr. eds. Aspartame Physiology and Biochemistry. New York, NY: Marcel Dekker 1984: 481-492.

32. Sturtevant RP., Sturtevant FM., Pauly JE., Scheving LE. Chronopharmacokinetics of ethanol. III. Variation in rate of ethanolemia decay in human subjects. Internat. J. Clin. Pharmacol. Biopharm. 1978; 16: 594-599.

33. Tephly TR., McMartin KE. Methanol metabolism and toxicity. In: Stegink LD., Filer LJ. Jr. eds. Aspartame Physiology and Biochemistry. New York, NY: Marcel Dekker 1984: 111-146.

34. Tephly TR., Watkins WD., Goodman JI. The biochemical toxicology of methanol. Essays Toxicol. 1974; 5: 149-177.

35. US Dept. of Health and Human Services. Third Annual Report on Carcinogens, PB:33-135855. Springfield, VA: National Technical Information Service, 1982.

36. Wilson RC., Knobil E. Acute effects of N-methyl-DL-aspartate on the release of pituitary gonadotropins and prolactin in the adult female Rhesus monkey. Brain Res. 1982; 248: 177-179.

37. Wimer WW., Russell JA., Kaplan HL. Alcohols Toxicology. Park Ridge, NJ: Noyes Data Corp., 1983.

38. Wurtman RJ. Neurochemical changes following high-dose aspartame with dietary carbohydrates. New Engl. J. Med. 1983; 309: 429-430.

39. Infurna R., Schubin W., Weiss B. Developmental toxicology of methanol. Toxicologist 1981; 1: 32.

Received: 06/10/85
Accepted: 07/16/85

NOTE The article "Aspartame--A New Food Ingredient Reply to the Critical Comments of Woodrow C. Monte" by Dr. Sturtevant represents the views of the author and are not necessarily those of the publishers or the Editor or Editorial Board. This of course is true of all articles published in this journal. Comments, either pro or con are accepted and if pertinent and of interest to our readers, will be published in our journal.

Dr. James W. Robinson, Editor

Journal of Environmental Science and Health
Part A: Environmental Science and Engineering
Part B: Pesticides, Food Contaminants, and Agricultural Wastes
Part C: Environmental Carcinogenesis Reviews

Part A: Environmental Science and Engineering

Emphasizes engineering innovations, control systems, laws, chemical fate of pollutants, and pollution levels and sources for the benefit of planners; industrial managers; public policy administrators; and design, civil, mechanical, industrial, and environmental engineers.

Part B: Pesticides, Food Contaminants, and Agricultural Wastes

Provides a common focal point for scientific papers from all pertinent disciplines concerning pesticides, food contaminants (natural and additive), and agricultural wastes. Researchers, scientists, and technologists whose work involves any of these areas will find a wealth of new and stimulating information in this journal. It also encompasses the developments in integrated methods of pest control, ecological implications, and economics of using pesticides.

Part C: Environmental Carcinogenesis Reviews

This important addition to the carcinogenesis literature provides multidisciplinary, concise, integrative, critical reviews convering *all* aspects of chemical carcinogens in the environment. Among the timely, topical subjects explored are reviews of specific compounds of compound classes of special interest . . . synergism and antagonism . . . theoretical models . . . and many, many more!

ORDER FORM

JOURNAL OF ENVIRONMENTAL SCIENCE AND HEALTH

Part A: Environmental Science and Engineering	Volume 20, 8 numbers
Part B: Pesticides, Food Contaminents, and Agricultural Wastes	Volume 20, 6 numbers
Part C: Environmental Carcinogenesis Reviews	Volume 3, 2 numbers

RATES (check one or more)	Part A		Part B		Part C	
Institutional	$189.75		$175.00		$49.50	
Individual	$94.88		$87.50		$24.75	
Foreign surface postage surcharge	$22.00		$22.50		$5.50	
Foreign air postage surcharge to Europe	$28.80		$21.60		$7.20	
Foreign air postage surcharge to Asia	$35.20		$24.60		$8.80	

All subscriptions must be prepaid. Payment must be made in U.S. currency.

Please enter my subscription to: ☐ Part A ☐ Part B ☐ Part C

I enclose payment by:

☐ Check ☐ Money Order in the amount of $ _____

☐ Visa ☐ Master Card ☐ American Express No._____

Exp. Date_____ Master Card four digit interbank No._____

Signature _____
(must accompany credit card payment)

Name _____

Address _____

City _____ State _____ Zip _____

☐ Please send me a complimentary copy of this journal: _____.

Please recommend library acquisition of this and all materials needed for teaching and research.

MAIL TO: **MARCEL DEKKER, INC.**
PROMOTION DEPARTMENT
270 MADISON AVENUE
NEW YORK, NEW YORK 10016

JESABC-R85