DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

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From Acting Chief, Epidemiology Branch (HFS-728)
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Subject Summary of adverse reactions attributed to Aspartame

To Health Hazard Evaluation Board

The Centers for Disease Control and Prevention forwarded 649 complaints of adverse reactions attributed to aspartame from before 1985. These complaints are generally not included in FDA summaries of adverse reactions attributed to aspartame because of differences in the information collected. Excluding the CDC data; between 1985 and 1993, CFSAN received 6239 complaints describing adverse reactions attributed to aspartame. Complaints were received from sources including consumers who contacted FDA directly, via the Nutrasweet (Searle) Company, Aspartame Consumer Safety Network, the 700 Club, health professionals, and other interested parties.

For the 4152 (66.5%) complainants providing information on gender, 3172 (76.4%) were female, 980 (23.6%) were male. For 3099 (50%) complainants whose ages were provided, the peak age group for reports was 30-39 years old, with 815 (26.2%) complaints. All other ten year age groups provided less than 20% of complaints.

For the 4206 (67.4%) complaints that included information on intensity of the reaction, 481 (11.4%) reactions were classified as severe and 3725 (88.6%) were classified as mild to moderate.

In some reports, adverse reactions were attributed to more than one product type. Diet soft drinks were implicated most frequently; with a total of 2854 (45.7%) complaints, followed by 1506 (24.1%) complaints attributed to table-top sweeteners. Each remaining product type was mentioned in less than 10% of all Aspartame complaints (Table 1).

Many complainants described multiple symptoms associated with aspartame. Almost 90 symptoms were described in total; with headache 1583 (25.4%) most frequent, followed by dizziness and problems with balance 674 (10.8%), change in mood quality or level 594 (9.5%), vomiting and nausea 560 (9.0%), abdominal pain 384 (6.2%), and change in vision 323 (5.2%). Other symptoms were reported by less than 5% of complainants (Table 2).

Of the 3923 (62.8%) reactions that could be classified in terms of consistency of the reaction following ingestion of aspartame, 1290 (32.9%) were Group A or episodic events, that occurred after consumption of various products containing Aspartame. An additional 1088 (27.7%) complaints were classified as Group B reactions, occurring on multiple occasions but associated with a specific Aspartame-containing product. A total of 691 (17.6%) reports were classified as group C reactions, with a single episode following consumption of Aspartame-containing products. The remaining 854 (21.8%) reports were classified as Group D, because the adverse reaction did not occur every time the complainant consumed the aspartame-containing product associated with the complaint, or the reaction was deemed unlikely to have been associated with aspartame.

There has been a gradual decrease in complaints of adverse reactions to aspartame received by FDA. The trend for reports of adverse reactions to Aspartame has declined from a 1985 peak, when 1510 reports were received to 261 reported reactions for 1993 (Figure 1.).

In summary, the number of adverse reaction complaints received by the FDA; and the nature of these reports in terms of demographic distribution, severity, strength of association with the product, and symptoms remain comparable to those from previous analyses.

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Evaluation of Consumer Complaints Related to Aspartame Use

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CONTENTS

INTRODUCTION

In February 1984, the Food and Drug Administration (FDA) requested the assistance of the Centers for Disease Control (CDC) in evaluating consumer complaints related to aspartame consumption. Up until that time the FDA had received over 100 complaints of various symptoms believed by the complainants to be related to their consumption of aspartame-containing products. Additional reports were known to be in the hands of G. D. Searle and Company, the manufacturer of aspartame, and in the hands of scientists concerned with the product's safety. Questions raised by some scientists and the public concern that developed in response to adverse publicity following the decision in July 1983 to permit aspartame's inclusion in soft drinks led the FDA to collect for analysis the reports of adverse reactions held by these other groups.

The report that follows includes the analysis of approximately 600 consumer complaints reported originally to the FDA, to G. D. Searle and Company, and to several other persons and private organizations. Over 200 of these complaints were analyzed in depth to assess their likelihood of being related to aspartame consumption. In most instances the complaints were consumer- initiated and were unassociated with physician evaluation or systematic testing. Therefore, the conclusions that can be drawn are limited regarding whether the conditions reported are or are not directly related to the aspartame ingestion. This report provides a description of the symptoms reported and the characteristics of the persons reporting them.

In addition, the report suggests a framework within which additional studies, should they be deemed necessary, could be undertaken to shed light on whether the reported symptoms were in fact due to ingestion of products containing aspartame.

BACKGROUND

Aspartame's use as a sweetener was originally approved by the FDA in 1974. However, based on objections to the approval and on requests for a hearing to investigate certain alleged toxic effects of aspartame, the FDA subsequently suspended the approval and conducted an extensive audit of various toxicological studies. Following the audit, a public board of inquiry consisting of scientists outside the FDA reviewed testimony and evaluated the scientific issues raised in the objections. Finally, in July 1981 the Commissioner of the Food and Drug Administration reviewed the Board's conclusions and determined that, on the basis of available data, aspartame consumption was safe within the meaning of the Federal Food, Drug, and Cosmetic Act. The major issues at the time of this earlier review were that aspartame consumption might cause brain damage (such as mental retardation), endocrine dysfunction, or tumors. There was little concern presented regarding possible acute symptomatology. Further, from the clinical studies performed by the sponsor prior to approval, there was little to suggest that acute effects were likely to occur.

In October 1981 the FDA reinstated its original approval for the use of aspartame as a table-top sweetener and in certain other products. In July of 1983 the approval was amended to permit the additional use of aspartame as a sweetener in carbonated beverages. Subsequent to the amended approval. there was an increase in the number of consumer complaints received. Much of this increase was concurrent with an increase in publicity about the FDA decision to permit aspartame's use in carbonated beverages, the increase stemming from various persons and agencies concerned with the safety of aspartame. Although aspartame is presently permitted in the United Kingdom and Canada, apparently there have been few reported complaints there.

Extensive scientific literature exists that reviews the physiological, biological, and toxicological effects of phenylalanine, aspartic acid, and methanol. Aspartame is broken down in the body to amino acids (phenylalanine and aspartic acid) and to methanol. During storage, varying amounts of the degradation product, a diketopiperazine (DKP), are formed. The effects of these breakdown products have remained a concern of some scientists.

The sponsor, G. D. Searle and Company, conducted a series of animal and clinical tests including studies specifically designed to assess the safety of the DKP breakdown product. A number of studies that have been reported examine the biological and biochemical effects of aspartame in humans. Relatively few of these studies were directed specifically at examining side effects or associated symptoms among people given large or even routine amounts in controlled situations.

INTERPRETATION OF FINDINGS

The interpretation of findings here presented is based on the results of the investigation found in later sections of this document.

This investigation into the consumer complaints received by the FDA and other organizations and individuals regarding symptoms considered by the complainants to have been caused by ingestion of aspartame-containing products had three major purposes. The first was to provide a basic descriptive analysis of the types of symptoms reported and the characteristics of the population reporting them. The second was to attempt to determine whether specific individual symptoms or constellations of symptoms were reported with sufficient consistency to suggest which, if any, of the reports had a likelihood of truly being caused by ingestion of aspartame-containing products. The third major purpose was to indicate areas where further studies, should they seem necessary, would be most likely to shed light on whether or not aspartame causes the symptoms reported.

It was not anticipated that this investigation alone could definitively establish whether ingestion of aspartame-containing products did or did not cause the symptoms reported. Definitive analyses and conclusions relative to causation are typically beyond the scope of information that can be collected by passive surveillance systems such as those where consumers are encouraged to report complaints and concerns regarding products they have used. Data from passive surveillance systems can, however, indicate the possibility of an association. In this discussion we will describe some of the strengths and limitations of such systems and the data they are able to provide, and how the limitations of such systems affect the conclusions that can be drawn from investigations such as the present study. Taking these limitations into

account, we will indicate which conclusions are most strongly suggested by the data together with potential alternative conclusions.

Passive surveillance systems

Passive surveillance implies that cases or reports are not actively solicited by the agency or organization concerned, but rather are initiated on the part of the consumer or complainant. The major strengths of such a passive surveillance system are, in addition to conserving resources, that there is no presupposition that certain foodstuffs or additives are more likely than others to cause difficulties, nor that certain conditions are more likely to be caused by a given product. Conversely, in an active system, unanticipated problems are less likely to be detected than ideally would be the case, because investigations are targeted toward specific products, agents, or conditions.

There are several underlying assumptions with regard to passive systems. One is that serious problems have a higher likelihood of being reported than do mild ones, even if the serious ones occur less commonly. Also, it is expected that symptoms and conditions that occur soon after use of the product are more apt to be thought by the consumer to be caused by the use of the product and, hence, reported. A third underlying assumption is that complaints regarding symptoms or conditions that occur commonly in the population are more likely to occur as a chance temporal association with consumption of the product than are more rare and serious symptoms. It follows then that these passive surveillance systems are thought to be more sensitive in their ability to detect rare and serious conditions occurring shortly after the use of a product than common symptoms or symptoms occurring at some distant time from the use.

Finally it is well accepted that such systems cannot, by themselves, prove that a given symptom or condition is caused by the use of a product, nor can they exonerate product use as a cause. Rather, their purpose is to permit any unusual clustering of reports to be detected. The descriptive analysis of the case reports can also be used to define whether further investigations may be needed and to identify those groups and conditions that, on further study, would be most likely to yield substantial new insights on the issue.

The attendant media publicity regarding the decision to permit the use of aspartame in carbonated beverages and the extensive public attention given to the various hearings concerning aspartame's safety add an additional difficulty to this particular investigation. Publicity regarding aspartame can be expected to increase the number of reports of both serious and common symptoms. It is likely that many of the latter will be temporally associated with aspartame ingestion by chance alone. Thus, while the publicity may have facilitated case finding by encouraging individuals with potentially valid complaints to report, it probably also contributed to an overall dilution of these complaints with a number of less specific and diffuse reports. This makes more difficult the task of identifying those individual symptoms or constellations of symptoms that may be likely to be related to the ingestion of products containing aspartame.

General Findings

Demographically, the most striking finding was the high prevalence of complainants who were white women, 20-60 years of age. Approximately 60 percent of all complainants fit this category. (The symptoms of the female complainants were distributed throughout all major symptom categories.) The information available does not permit us to determine whether the

over-representation of women among the complainants reflects 1) the possibility that women in this age group are more likely to use products containing aspartame or more likely to use them more frequently, thus increasing the exposure of this subpopulation; 2) a greater tendency to follow through and report despite equal susceptibility; or 3) a greater susceptibility to side effects from aspartame use. However, since it seems possible that women may be more likely to be users of low-calorie products than men, it may at least partially account for the fact that there are substantially more women reporting side effects than men. Similarly the other associations by race and age also may reflect differences in use pattern more than they do differences in susceptibility. The inherent characteristics of passive reporting systems with self-selected complainants make the definition of group-specific differences difficult. Some differences in subgroup reporting rates are to be expected; large differences, however, could be used to focus later investigations.

Though information was obtained with regard to the specific aspartame-containing products that were associated with symptoms, it was not possible to determine if any individual product was more likely to be reported than others. There is large variety of aspartame-containing products, and no information was available to us regarding patterns of use, frequency of use, amount purchased, etc. In addition, the publicity surrounding the recent inclusion of aspartame in carbonated beverages may have affected public perception as to which type of product(s) were more likely to be of concern, an effect that we could neither assess nor control for in analysis. The inability of this type of study to implicate specific products would not seem to present a serious problem in this case. There has been relatively little

concern directed at specific products; rather, most of the concerns have focused on aspartame itself, regardless of the product used.

Criteria for Assessing Possible Adverse Reactions

Because we were unable to identify published criteria for determining when given symptoms (as distinct from pathological entities) are caused by ingestion of foodstuffs or additives, it seemed reasonable to determine if the type of approach used to assess adverse reactions to medications could be adapted for use concerning aspartame. Often with medications, relatively uncommon adverse effects are recognized only after the product is approved for public use.

In pharmacotherapy, therapeutic claims are customarily verified by using double-blind, randomized clinical trials (RCTs) as the research standard. In these studies patients of equal clinical susceptibility to either recovery or adverse events are randomly selected to be given a medication in appropriate dosage or a control "placebo" treatment, and outcomes are carefully monitored. In order to guard against inadvertent bias on the part of either the investigator or the patient, neither can be aware of whether the patient will be given the therapeutic agent under consideration or the control therapy. These safeguards are to prevent both the patient and the investigator from inadvertently overinterpreting possible improvements due to one therapy versus another. The standard of the double-blind randomized clinical trial has now been well accepted in the field of pharmacotherapy and is required prior to licensure of new drugs despite the fact that such trials are often expensive and may require elaborate strategies to insure that both the patient and the investigator remain unaware of which therapy the patient is actually receiving.

This standard, however, is rarely able to be adhered to for the evaluation of adverse reactions from medications. Rather, publication of case reports and the accumulation of such reports remain an important means for identifying such reactions. Evaluation of symptoms thought to be related to the ingestion of certain foods is quite similar conceptually to the evaluation of symptoms thought to be related to exposure to medications. However, key differences remain. Certainly for prescription medications, the physician is the most common source of the report. Furthermore, in the case of prescription medications, the report can more easily be placed in the context of other illnesses that the patient may have and other exposures potentially able to cause similar symptoms. For food additives, on the other hand, the source of the report is usually the persons who experienced the symptoms. Further, they may not have the detailed knowledge regarding their illnesses and exposures that would permit them to evaluate the possible existence of alternative explanations.

Nevertheless, because of this conceptual similarity and the similarity in the process by which scientific knowledge is developed, we examined the consumer complaints received regarding possible effects of aspartame use according to the principles outlined by Kramer and Hutchinson.[1,2] In their attempt to develop standards to improve the scientific precision in the diagnosis of adverse drug reactions, they identified six issues that need to be evaluated to determine whether a given clinical manifestation is likely to be caused by the drug in question. Although obviously referring to information available to physicians caring for patients, these issues have clear relevance for the evaluation of the reports concerning aspartame ingestion.

The six issues they identified are presented below, modified for assessment of reactions to food additives.

(1) Previous general experience with the additive: Clinical manifestations widely accepted as being due to the suspected additive are weighted more heavily than those previously unknown. Unfortunately, there have been few studies that were directed specifically at examining side effects or symptoms among aspartame users. In one small double-blind randomized clinical trial of aspartame use in a weight loss program,[3] the authors reported no difference in prevalence of symptoms among those given aspartame and those given a placebo. Indeed, headaches and abdominal cramps, two of the more frequently reported symptoms, were, if anything, slightly more common among the placebo users. However, in another trial conducted in pre-marketing testing, the aspartame group reported more complaints than did the placebo group.[4] Otherwise, too little is known to permit us to consider one group of symptoms more heavily than others.

(2) Alternative etiologic candidates as possible causes of the clinical manifestation reported: High among these candidates are possible medications that the complainant may be taking and/or other illnesses or conditions that may cause the symptoms themselves. This information is often available to physicians assessing possible adverse reactions to medications, but it is likely to be only incompletely available from the complainants themselves, even after the reinterview. Due to the limited historical information, therefore, we were essentially unable to evaluate adequately the likelihood of alternative causes for the symptoms reported. We did exclude patients who indicated that, upon consultation, their physician believed that other factors were the cause or that aspartame was not the cause (Group D complainants).

The remainder of the reports were included in the analysis because of concern that complaints could be inappropriately dismissed with only the historical information available. Additionally, the requirement that Group A complainants must have been rechallenged with different aspartame-containing products was instituted to distinguish symptoms potentially caused by ingredients other than aspartame in specific products from symptoms potentially caused by the aspartame in those products.

(3) The timing of the manifestation: Again, in regard to medications, records are available as to when exposure began. Further, persons under a physician's care are more likely to take notice of the presence of new symptoms than are persons consuming a food additive as part of their daily routine. Thus, in many of the reports relating to aspartame consumption, particularly for diffuse symptoms, the details regarding initiation of consumption and initiation of symptoms are unclear. However, most of the reported symptoms occurred within a relatively short interval from last consumption of aspartame-containing product(s), and thus the reported time frames are consistent with the possibility that they are caused by ingestion of aspartame-containing products. A few complainants did report multiple discrete episodes, giving clear, precise histories of the temporal relations.

(4) Evidence of overdose or excess consumption: Few of the complainants gave histories of unusually high consumption. Some did describe the appearance of their symptoms as occurring after consuming more than their usual amounts and not occurring when they consumed smaller amounts. A related issue is that of inappropriate use. Aspartame is not meant to be used in cooking or baking. Since few of the complainants indicated that they did this, inappropriate use does not appear to be a likely source for the majority of the complaints.

(5 and 6) Effects of cessation and rechallenge: This is the most important criterion used in this report: the observation of whether the clinical manifestations abate after cessation of use of the food additive and whether they recur upon reuse. A substantial amount of effort was spent on the part of the field investigators in assessing whether symptoms recurred on rechallenge with the same or other aspartame-containing products. It was felt that persons who experienced recurrences upon reuse after a distinct symptom-free period had a higher likelihood of having their symptoms actually being due to ingestion of aspartame. While, in general, we feel this to be true, there are substantial limitations in applying this criterion. People who experience symptoms after first use might be primed to experience them on repeated uses. Avoiding the bias engendered by such priming is one of the chief reasons for the use of the double-blind methods in clinical trials.

Thus, because of data limitations intrinsic to the use of personal reports of symptoms without independent evaluation, many of the recommended criteria for assessing whether a particular clinical manifestation is attributable to a drug or food additive could not be fully utilized. This is especially so with regard to the criteria of previous experience with reactions and alternative etiologic candidates for the symptoms reported. For many of the reports, the timing was within acceptable limits for plausibility so that few cases could be excluded on this basis. In only a few instances was evidence available to suggest misuse or overuse of aspartame-containing products. Thus, only the issue of challenge and rechallenge was able to be reasonably and thoroughly assessed. One risk with this approach, however, is that if complainants believe that particularly serious or unpleasant clinical manifestations were due to aspartame consumption, they would be highly unlikely to use it again.

Possible Future Investigations

The number of instances of persons challenging themselves several times with aspartame-containing products and reporting symptoms with each rechallenge suggests that some individuals may be sensitive. The only way to clearly determine this is through focused clinical studies. Because of the numbers of reports, the subtlety and potential seriousness of some of the manifestations, the concerns of some scientists, and the possibility that one complainant has had his symptoms of hyperactivity verified on independent exam, it would seem that the highest priority for any future investigations might be in the neurological/behavioral area, focusing on such symptoms as headaches, mood alterations, and behavior changes.

METHODS

Initial review of the consumer complaint reports received by the FDA indicated that important details of complainant characteristics, symptoms, and recurrence of symptoms in the same individual were unavailable for many of the reports. Therefore, a more detailed, standardized questionnaire was developed to enable the FDA field staff to interview all complainants in a focused and standardized fashion. Interviews were conducted either in person or by telephone. If the complainant had visited a physician, the investigator also interviewed the physician and requested a copy of the medical records. Simultaneously with these efforts, the FDA contacted G. D. Searle and Company as well as others known to have received complaints regarding possible adverse reactions to aspartame so that they could include these reports in the investigation.

When the field staff completed the interviews, the questonnaires were sent to the FDA main office in Washington where they were logged in and given an identifying number. The forms were reviewed by the FDA staff for completeness, clarity, and legibility; copies were then sent to the CDC for further review, coding, and computerization.

Reports Analyzed

Six hundred forty-five initial contacts are included in this report. These included all complaints received by the FDA before April 16, 1984; those complaints received by G. D. Searle and Company until February 24, 1984; and the complaints received by private scientists (principally Woodrow C. Monte, Director, Food Science and Nutrition Laboratory, Arizona State University, Tempe, Arizona). A number of the reports from this last group were received later in the investigation; some were received after March 1.

The field investigators contacted each complainant and, where applicable, interviewed any additional family members who reported adverse effects. In addition, if the complainant had received medical care, field investigaors interviewed the attending physician, and medical records were sent to CDC with the complainant's questionnaire. Complainants who refused to be interviewed or were unable to be contacted were excluded from analysis. Also, complaints that were withdrawn because the complainant no longer believed the symptoms were due to aspartame were not analyzed as well as complaints that were determined not to be associated with actual aspartame use (e.g. letter of inquiry, etc.).

Screening Definitions

For the purposes of this study, a case was defined as any report of symptoms that the complainant associated with aspartame use. All cases meeting this definition were tabulated regarding basic demographic information, major symptoms, State of residence, and agency or person that received their original complaint. Cases involving symptoms that were reported very infrequently or for which no biologically plausible mechanism could be postulated were not analyzed further (Table 5-8). The remaining case reports were classified into the most frequently occurring symptom categories: neurological/behavioral, gastrointestinal, allergic, and menstrual.

Many persons reported symptoms from more than one category; in these cases the symptoms were analyzed separately by each category. Thus, the sum of the cases from the various sections in the report will equal more than the number of persons registering complaints. If the symptoms from one category were clearly secondary to another (for example, the nausea associated with migraine-type headache) symptoms were analyzed in the primary category only.

In a few cases, the complainant reported consuming a product containing aspartame prior to the release of the product on the market. Because some interviews were conducted several months after the episodes occurred and because of the problems inherent in asking consumers to recall distant dates accurately, we did not attempt to screen and reject these cases but included them in the analysis, listing the date as unknown if a conflict was noted.

Detailed Analysis

We reviewed the first 231 interviewed cases that were received and fully coded at CDC by June 15. One CDC investigator coded each case according to a system that included the time frame for the occurrence of symptoms and symptom complex. A second investigator then recoded each case. We compared results, discussed discrepancies, and made a joint decision as to the classification of each. By this process 199 cases were classified as containing reports of symptoms from four symptom categories: neurological/behavioral, gastrointestinal, allergic, and menstrual.

Special attention was paid to the temporal association between aspartame ingestion and onset of symptoms. The operating hypothesis was that symptoms associated with aspartame ingestion would be more likely to show a consistent temporal pattern relative to the time of the ingestion of the products containing aspartame. The following time frames were defined:

Latency Interval: Time from the most recent ingestion to onset of symptoms.

Duration of Symptoms: The time over which symptoms occurred after a single discrete ingestion. Duration of symptoms was examined when the complainant did not repeat ingestion during the symptomatic period. In situations where symptoms could not be associated with a single discrete ingestion, the duration of the episode was recorded as unknown.

Symptom-free Interval: The time from date of first regular ingestion of the implicated product(s) containing aspartame to date of symptom onset. This refers to a symptom-free period when the complainant used aspartame-containing products(s). In some cases this time period is necessarily the same as the latency interval. For menstrual complaints, date of first symptoms was calculated as actual or expected date of menstrual period.

Time from Last Ingestion to the Cessation of Symptoms: Time from last reported ingestion of implicated aspartame-containing product(s) to the complete cessation of symptoms. For menstrual complaints, the date of cessation of symptoms was calculated from the date of the first normal period following menstrual symptoms.

These four time periods were chosen because many of the complainants could not identify a discrete ingestion of product(s) containing aspartame that was associated with a well delineated, acute symptom episode. For example, many of the reports were of chronic symptoms associated with continuous ingestions. It was for this type of complaint that the last two time periods were primarily intended.

To help detect any more consistent associations, we then defined a series of screening criteria to select those likely to be most fruitful for further analysis. To accomplish this, we classified cases according to a scale based on elements of the history characterizing the relative likelihood that reported symptoms were due to ingestion of product(s) containing aspartame. The screening classification scale was as follows:

Group A: Symptoms recurred each time the complainant consumed more than one product containing aspartame. Placement into Group A required that there be a symptom-free period in which no aspartame-containing

products were consumed, followed by another period of symptoms associated with a different aspartame-containing product (see note following Group B).

Group B: Symptoms recurred each time the complainant consumed the same product containing aspartame. As in Group A, there must have been a totally symptom-free period between ingestions (see note following).

Note: Cases in which the complainant volunteered that the symptoms did not recur with the ingestion of small quantities of products containing aspartame but did recur with larger quantities were categorized as Group A or Group B depending on whether the recurrence was with different or with the same products containing aspartame.

Group C: Symptoms were associated with the ingestion of products containing aspartame, but the complainants did not consume the products again.

Group D: Symptoms did not recur every time the complainant consumed a products containing aspartame. Also placed in this Group were complainants who consulted physicians who stated that the symptoms were unlikely to be due to aspartame. In order not to obscure the analysis of temporal data with data from cases felt to be unlikely to be related to aspartame ingestion, Group D cases were not analyzed regarding the temporal period between the previously reported symptoms and ingestion.

Throughout this report, we will use "rechallenge" to mean second or subsequent ingestion of a product or products containing aspartame after a symptom-free interval.

As part of a quality control process, all persons in Group A and selected persons in Groups B and C (based on seriousness of symptoms and/or cogency of complaints) were reinterviewed by one of the authors of this report to obtain further details and to confirm their challenge/rechallenge history. We used these cases to develop our case report summaries for each symptom category.

In addition to providing a basis for the case report summaries, the reinterview procedure and the associated case reviews also contributed to the refinement of the preliminary computer data analysis. Prior to the reinterviews, we used computer analysis to obtain preliminary frequency tabulations for screening purposes. During these interviews, we found that complainants frequently offered additional and sometimes conflicting information about their symptoms. Also, in the process of reinterviewing the complainants, we refined some of the analytic categories used during the preliminary computer screening procedure. Thus, the review process was also used to clarify the preliminary data obtained during the computer screening procedure.

Finally, we compared the first 231 reports with those from the remaining persons who were interviewed later but not included in the in-depth analysis with the FDA log of demographic characteristics and major symptoms. We did this to insure that the persons included in the in-depth analyses were similar in major demographic or symptom characteristics to those not analyzed in depth (Appendix I).

OVERVIEW RESULTS

Completion Rates

After soliciting reports from G. D. Searle and Company and from Woodrow C. Monte, the FDA initiated--beginning on February 24, 1984--the intensive follow-up of consumer complaints. The reports received from Searle and Dr. Monte were combined with reports received by the FDA through April 16, 1984, to make a total of 645 consumer complaints. These complaints were designated for follow-up by the FDA field investigators. Of the initial 645 consumer contacts, 31 complainants withdrew their complaint and 22 were actually other types of contacts such as inquiries not associated with symptoms. Of the remaining 592 complaints, 42 were not followed up, primarily because of inability to locate the complainant; 33 of the complainants refused further interview. Thus a total of 517 completed questionnaires (87 percent of the 592 complaints) were available for review.

Questionnaires received at CDC were coded for intensive computer analysis. The remaining 286 questionnaires received later at CDC were assessed for comparability with the first 231. The results of this comparative analysis are found in Appendix I.

The following data are based on the first 231 cases until otherwise noted.

Demographic

Overall, the complainants were predominantly female (75 percent) and white (94 percent) (Tables 5-1 and 5-2). The majority of complainants (77 percent) were aged 21-60 years (Table 5-3). There were 17 reports on children below the age of 16, 10 of whom were male. The youngest age reported was 4 months, while the oldest was 77 years. Overall, the complainants in this study population were approximately one and one-half times more likely to be women,

and were two and one-half times more likely to be women between the ages of 20 and 59 than would be expected from the 1980 census population estimates.

The reports came from all sections of the country, with the greatest number of reports coming generally from the more populous states such as New York and California (Table 5-4).

The 231 consumer complaints that were analyzed were originally submitted to a variety of agencies and individuals. The FDA received 124 of the reports; G. D. Searle and Company received 91 reports. Dr. Woodrow Monte forwarded 13 consumer complaints that had been originally submitted to him. The remaining three reports came first to Mr. James C. Turner, Counselor, Community Nutrition Institute, Washington, D.C. (Table 5-5).

The number and variety of reported symptoms was large, with 63 percent of the complainants reporting multiple symptoms (Table 5-6) and 15 percent of the complainants reporting symptoms from more than one symptom category (Table 5-7).

Thirty-two cases with complaints that were reported very infrequently or for which there was no biologic plausibility were excluded from further analysis beyond the tabulation of demographic characteristics. Symptoms reported by these complainants are presented in Table 5-8. Subsequent analyses are based only on the 199 fully reviewed cases.

Table 5-9 shows the distribution of cases by screening classification. Overall, 13 percent of all cases were classified as belonging to Group A. As defined earlier in the report, these are cases in which rechallenges with different aspartame-containing products were associated with repeat onset of symptoms. Some 15 percent of cases were classified into Group B--symptoms reported to recur on rechallenge to the same product--while the largest

proportion of symptoms, 41 percent, were classified into Group C, in which no history of a rechallenge was available. Thirty-two percent of the cases fell into the D category, cases in which the physician stated that the symptoms probably had a different etiology, or cases in which the complainant had subsequently consumed aspartame without recurrence of symptoms.

Symptoms were reported to occur in association with all major aspartame-containing products on the market at the time of the report (Table 5-10). The most frequent product type named was the table-top sweetener Equal©* (38 percent of implicated products), but this was followed by soft drinks sweetened with aspartame (26 percent of implicated products).

The first month that symptoms were reported to have occurred was July 1982.† There were relatively few symptoms reported, however, until the summer of 1983. This was followed by another peak of reported symptoms in the winter of 1984 (Table 5-11).

Overall, 19 percent of complainants reported that they had not seen a physician for any medical problems in the past two years. Of the remaining 81 percent, the most frequent preexisting medical complaints were allergies, hypertension, and diabetes. There were no complaints filed by individuals with a personal or family history of phenylketonuria. Use of medications (including over-the-counter drugs) were reported by 72 percent of the complainants, with antihypertensives, vitamins, and analgesics being reported most frequently.

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*Use of trade names is for identification only, and does not constitute endorsement by the Department of Health and Human Services or any of its agencies.

†This excludes one case who reported symptoms occurring in June, 1981, when aspartame was not on the market.

OVERVIEW TABLES: CASES REVIEWED BY CDC

Table 5-1

Sex Distribution of Cases Selected for Review

Sex	Cases	
	Percent	Number
Male	25%	58
Female	75%	173
TOTAL	100%	231

Table 5-2

Race Distribution of Cases Selected for Review

Race	Cases	
	Percent	Number
White	94%	218
All Other	3%	6
Unknown	3%	7
TOTAL	100%	231

Table 5-3

Age Distribution of Cases Selected for Review

Age (Years)	Cases	
	Percent	Number
≤1 - 10	5%	12
11 - 20	4%	10
21 - 30	18%	42
31 - 40	26%	60
41 - 50	20%	46
51 - 60	13%	31
61 +	11%	25
Unknown	2%	5
TOTAL*	99%	231

*Percent (%) may not total 100 due to rounding.

Table 5–4

Distribution of Cases Selected for Review By State of Residence

State	Cases	
	Percent	Number
NY	15%	34
CA	11%	25
PA	6%	14
MI	6%	13
NJ	5%	12
OH	5%	12
IL	5%	11
MD	4%	10
FL	3%	7
MA	3%	7
NC	3%	7
TX	3%	7
VA	3%	7
WI	3%	7
IN	3%	6
MS	3%	6
AZ	2%	5
CT	2%	5
KS	2%	5
CO	2%	4
KY	1%	3
OK	1%	3
AL	1%	2
MN	1%	2
NH	1%	2
DC	<1%	1
GA	<1%	1
LA	<1%	1
MT	<1%	1
NE	<1%	1
RI	<1%	1
SC	<1%	1
TN	<1%	1
WA	<1%	1
WV	<1%	1
Unknown	2%	5
TOTAL		231

Table 5-5

Distribution of Cases Selected for Review
By Agency/Individual Receiving Report

	Cases	
	Percent	Number
Food and Drug Administration	54%	124
G. D. Searle and Company	39%	91
Woodrow C. Monte	6%	13
James C. Turner	1%	3
TOTAL	100%	231

Table 5-6

Distribution by Number of Symptoms

Number of Symptoms	Cases	
	Percent	Number
1	37%	85
2	26%	61
3	18%	42
4	8%	19
5	7%	16
≥6	3%	8
TOTAL*	99%	231

*Percent (%) may not total 100 due to rounding.

Table 5-7

Distribution of Cases Reviewed in Depth*
By Major Symptom Categories

Symptom Category	Cases Percent	Number
Neurological/Behavioral Only	51%	101
Neurological/Behavioral + Gastrointestinal	8%	16
Neurological/Behavioral + Allergic	4%	7
Neurological/Behavioral + Menstrual	3%	5
Gastrointestinal Only	16%	32
Gastrointestinal + Allergic	1%	2
Allergic Only	16%	31
Menstrual Only	3%	5
TOTAL†	101%	199

*Excludes 32 cases with miscellaneous symptoms (Table 5-8).

†Percent (%) may not total 100 due to rounding.

Table 5-8

Frequency Distribution of Miscellaneous Symptoms
Accepted for Demographic Review Only

Complaint	Number
Elevated blood glucose*	5
Palpitations	3
Shortness of breath	1
Hyperventilation	1
Chest pain	1
Backache/pain	2
Arm pain	1
Chills/sweating	3
Cold symptoms	1
Cough	1
Skin blemish	1
Swollen hands/fingers	2
Swollen joints (in legs and groin)	1
Flushing of face	1
Burning tongue	1
"Hard to swallow"	1
Constant/severe hunger	1
Diminished sense of taste	1
Stiff jaws	1
Ears "clogged"	1
Cold fingertips	1
"Cerebrospinal fluid from nose"	1
Retinal bleeding	1
Melanoma	1
Abnormal cells (Pap test)	1
Increased/frequent urination	3
Burning sensation during urination	2
Urinary tract infection	1
Unable to urinate	1
TOTAL COMPLAINTS	42
TOTAL COMPLAINANTS	32

*Includes glycosuria.

Table 5-9

Distribution of Cases by Screening Classification*
Cases Reviewed in Depth Only†

Screening Classification	Cases Percent	Number
Group A	13%	26
Group B	15%	29
Group C	41%	81
Group D	32%	63
TOTAL§	101%	199

*Screening classifications:

Group A: Symptoms recurred on rechallenge with more than one aspartame-containing product

Group B: Symptoms recurred on rechallenge with same aspartame-containing product.

Group C: Symptoms occurred associated with aspartame-containing product, but there was no rechallenge.

Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.

(For complete definitions, see pages 17-18.)

†Excludes 32 cases with miscellaneous symptoms (Table 5-8).

§Percent (%) may not total 100 due to rounding.

Table 5-10

Distribution of Cases Reviewed in Depth
by Aspartame-Containing Products Implicated by Complainant*

Product	Percent	Number
Table-top Sweetener	38%	105
Diet Soft Drink	26%	72
Kool Aid ®	14%	39
Iced Teas	6%	17
Hot Chocolate	5%	15
Lemonades	4%	12
Puddings/Gelatins	3%	7
Punch Mix	3%	7
Other	1%	2
Unknown	0%	1
TOTAL	100%	277†

*Excludes 32 cases with miscellaneous symptoms (Table 5-8).

†Some complainants reported use of more than one product.

Table 5-11

Distribution of Cases Selected for Review by Date of Symptom Onset

	Cases	
	Percent	Number
1982		
July/August	3%	7
September/October	1%	3
November/December	3%	7
1983		
January/February	6%	14
March/April	6%	14
May/June	9%	20
July/August	23%	53
September/October	15%	35
November/December	10%	22
1984		
January/February	16%	36
March/April	3%	9
Unable to identify month of onset	4%	11*
TOTAL†	99%	231

*Includes one complaint in which the complainant was unsure of date of onset and estimated June 1981, at which time aspartame was not on market.

†Percent (%) may not total 100 due to rounding.

NEUROLOGICAL/BEHAVIORAL SYMPTOMS: RESULTS

Demographic Characteristics

The demographic characteristics of the 129 cases reporting neurological/behavioral symptoms alone or in combination with other symptom categories are similiar to the demographic characteristics of all cases combined. Over three-quarters (77 percent) are 21-60 years of age. The majority are white (98 percent) and female (72 percent) (Table 6-1). The demographic characteristics of Groups A-C, on whom the following analysis focuses, are similar to the demographic characteristics of the overall group of complainants with neurological/behavioral symptoms.

Classification

Of the 129 cases with neurological/behavioral symptoms, 15 percent (19) met the criteria for Group A, 12 percent (15) for Group B, 44 percent (57) for Group C, and 29 percent (38) for Group D (Table 6-2). Only Groups A, B, and C will be discussed in the following analysis in order not to obscure the analysis with data from cases felt to be unlikely to be related to aspartame ingestion.

Description of Symptoms

As can be seen in Table 6-3, a large number and variety of neurological/behavioral symptoms were reported. The most frequently reported single symptom was headache (22 percent). Mood alterations, which included complaints of anxiety, agitation, irritability, or depression, were reported by 21 percent of the complainants. Insomnia (11 percent), dizziness (10 percent) and fatigue (10 percent) were the next most frequently reported symptoms. There were five cases of seizure-type activity (3 percent) reported to be associated with aspartame ingestion. (These are reviewed in further

detail elsewhere--see pages 68-76). Many other types of neurological/ behavioral symptoms were reported and are enumerated in Table 6-3.

Temporal Associations between Symptoms and Aspartame Products

Symptom-free interval: Time from the first regular use of implicated aspartame product(s) to neurological/behavioral symptom(s). Data on the symptom-free intervals of the most frequent neurological/ behavioral symptom categories are presented in Tables 6-4 and 6-5. Information on hyperactivity is also included.

In general, cases with more specific, discrete symptoms such as headaches or dizziness tended to have shorter symptom-free intervals than those cases with more diffuse symptoms such as mood alterations or fatigue. For example, over half (59 percent) of the complainants reporting headaches reported that the headaches began less than a week after start of regular consumption of aspartame-containing product(s), and 41 percent reported that the headaches began on the same day use as first use. On the other hand, over half (54 percent) of the complainants reporting mood alterations stated that the symptoms did not begin until they had been using the product(s) for at least 1 week.

Latency interval: Time from most recent ingestion of implicated product to symptom onset. The latency intervals for headache, dizziness, and hyperactivity are included in Table 6-6. This information is not presented for insomnia, mood alterations or fatigue since it was quite often not possible for complainants with these symptoms to provide this information.

The latency intervals for headache, dizziness, and hyperactivity symptoms tend to be fairly short in duration, with the majority being less than 3 hours. This information, however, was often not available even for these

three symptoms. For example, in 37 percent of the reports of headaches and 53 percent of the reports of dizziness, the complainant could not provide this information.

Duration: Time over which symptom episode occurred. Duration was calculated only if a discrete ingestion could be identified (Table 6-7).

The majority of the reported episodes of headaches, for which this information was available, lasted 12 hours or less. Episodes of dizziness were generally of short duration also, with the majority of cases of known duration lasting less than 6 hours. Once again, this information was not available for a large number of the cases.

Post-ingestion symptomatic interval: Time from final ingestion of implicated product(s) to complete cessation of neurological/behavioral symptom(s) (Table 6-8).

When the complainant could not identify a discrete episode, the post-ingestion interval was calculated. The majority of the complainants reporting insomnia, mood alteration, or fatigue who could provide this information stated that their symptoms were gone within 6 days of ceasing to use products containing aspartame. One complainant in each of these categories reported still being symptomatic at the time of interview, even after stopping use of products containing aspartame.

Medical History

About one-third (36 percent) of the cases reported no medical problems for which they sought care in the past 2 years. The most frequent medical problems reported were allergies to foods, drugs, or other substances. Hypertension (8) and diabetes (7) were the next most frequently reported problems. Six neurological/behavioral illnesses were reported, including two

reports of previous seizure-type activity, one report of migraine headaches, one report of anxiety disorder, and one report of chronic schizophrenia.

Medications

Forty of the cases reported taking no medications in the past 2 years. Of the medications reported, the most frequently cited were antihypertensives (10). Fourteen other reported medications could be broadly considered as having neurological or behavioral effects. These medications included tranquilizers (4), analgesics/narcotics (4), antidepressives (2), sedatives (1), and antipsychotics (1).

Physician Contacts

In three-quarters of the cases no physician was consulted about the symptoms reported. Of the 25 percent who were seen by a physician, one physician (case report V-0002*) stated conclusively that he felt that the aspartame caused the symptomatology. Several other physicians felt that aspartame was possibly associated with the symptoms, but were not willing to make this diagnosis based on their evaluation of the symptom episode(s) (see case reports T-0346, V-0090, and M-0328*).

*Case reports follow on pages 53-69.

NEUROLOGICAL/BEHAVIORAL SYMPTOMS: TABLES

Table 6-1

Age, Race, and Sex Distribution of Cases With Primary Neurological/Behavioral Symptoms By Screening Classification

	All Cases* Selected for Review		Group D† Excluded	
	%	No.	%	No.
Age (Years)				
≤20	10%	13	11%	10
21-30	21%	27	20%	18
31-40	29%	37	30%	27
41-50	13%	17	12%	11
51-60	14%	18	15%	14
61+	11%	14	9%	8
Refused/Unknown	2%	3	3%	3
TOTAL	100%	129	100%	91
Race				
White	98%	126	97%	88
All Other	2%	2	2%	2
Unknown	1%	1	1%	1
TOTAL	101%	129	100%	91
Sex				
Male	28%	36	32%	28
Female	72%	93	69%	63
TOTAL§	100%	129	101%	91

*Excludes 2 cases with miscellaneous symptoms.

†Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame. (For complete definitions of Groups A-D, see pages 17-18.)

§Percent (%) may not total 100 due to rounding.

Table 6-2

Distribution of Cases Selected for Review
With Primary Neurological/Behavioral Symptoms*
By Screening Classification†

	Cases Selected for Review	
	Percent	Number
Group A	15%	19
Group B	12%	15
Group C	44%	57
Group D	29%	38
TOTAL	100%	129

*Excludes 2 cases with miscellaneous symptoms.

†Screening classifications:

Group A: Symptoms recurred on rechallenge with more than one aspartame-containing product.

Group B: Symptoms recurred on rechallenge with same aspartame-containing product.

Group C: Symptoms occurred associated with aspartame-containing product, but there was no rechallenge.

Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.

(For complete definitions of Groups A-D, see pages 17-18.)

Table 6-3

Distribution of Neurological/Behavioral Symptoms By Subcategory, Group D Excluded*

Symptoms	Percent	Number
Headache	22%	41
Mood Alterations	21%	39
Insomnia	11%	20
Dizziness	10%	19
Fatigue	10%	18
Visual Impairment	4%	8
Numbness	3%	6
Hyperactivity	3%	5
Seizures	3%	5
Disorientation	2%	4
Lack of Concentration	2%	3
Ringing in Ears	2%	3
Memory Loss	2%	3
Drowsiness/Listlessness	1%	2
Fainting	1%	1
"Hallucinations"	1%	1
Loss of Balance	1%	1
Motor Dysfunction	1%	1
Sleepwalking	1%	1
Speech Impairment	1%	1
"Rush to Forehead"	1%	1
"Paranoia"	1%	1
Nightmares	1%	1
TOTAL SYMPTOMS†	105%	185
TOTAL COMPLAINANTS	100%	91

*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.
(For complete definitions of Groups A-D, see pages 17-18.)

†Percent (%) may not total 100 due to rounding.

Table 6-4

Time From First Regular Use Of Implicated Aspartame-Containing Product(s)
To Neurological/Behavioral Symptoms
(Symptom-Free Interval)
By Reported Symptoms
Group D* Excluded

Time	Headache		Dizziness		Hyperactivity	
	%	No.	%	No.	%	No.
≤ 1 day	41%	17	42%	8	60%	3
2-6 days	17%	7	5%	1	0%	0
7-30 days	10%	4	11%	2	20%	1
1-2 months	7%	3	5%	1	0%	0
≥2 months	12%	5	32%	6	0%	0
Unknown	12%	5	5%	1	20%	1
TOTAL†	99%	41	100%	19	100%	5

*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.
(For complete definitions of Groups A-D, see pages 17-18.)

†Percent (%) may not total 100 due to rounding.

Table 6-5

Time From First Regular Use Of Implicated Aspartame-Containing Product(s)
To Neurological/Behavioral Symptoms
(Symptom-Free Interval)
By Reported Symptoms
Group D* Excluded

Time	Insomnia		Mood Alterations†		Fatigue	
	%	No.	%	No.	%	No.
≤ 1 day	15%	3	18%	7	6%	1
2-6 days	10%	2	15%	6	22%	4
7-30 days	20%	4	13%	5	11%	2
1-2 months	15%	3	18%	7	33%	6
≥2 months	20%	4	23%	9	22%	4
Unknown	20%	4	13%	5	6%	1
TOTAL	100%	20	100%	39	100%	18

*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.
(For complete definitions of Groups A-D, see pages 17-18.)

†Includes anxiety, irritation, agitation, and depression

Table 6-6

Latency Interval for Neurological/Behavioral Symptoms
Associated with Discrete Ingestion of Aspartame-Containing Products
By Reported Symptoms
Group D* Excluded

Time	Headache %	Headache No.	Dizziness %	Dizziness No.	Hyperactivity %	Hyperactivity No.
≤ 4 minutes	5%	2	11%	2	0%	0
5-30 minutes	10%	4	5%	1	0%	0
31 min. - 1 hour	15%	6	16%	3	40%	2
2-3 hours	10%	4	16%	3	20%	1
4-6 hours	10%	4	0%	0	20%	1
7-24 hours	7%	3	0%	0	0%	0
1-2 days	7%	3	0%	0	0%	0
Unknown/NA†	37%	15	53%	10	20%	1
TOTAL§	101%	41	101%	19	100%	5

*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.
(For complete definitions of Groups A-D, see pages 17-18.)

†Includes cases for which a discrete ingestion could not be identified.

§Percent (%) may not total 100 due to rounding.

Table 6-7

Duration of Neurological/Behavioral Symptoms Associated with Discrete Ingestion of Aspartame-Containing Products By Reported Symptoms Group D* Excluded

Time	Headache		Dizziness		Hyperactivity	
	%	No.	%	No.	%	No.
≤ 4 minutes	0%	0	0%	0	0%	0
5-30 minutes	2%	1	5%	1	0%	0
31 min. - 1 hour	2%	1	11%	2	0%	0
2-3 hours	12%	5	5%	1	20%	1
4-6 hours	10%	4	16%	3	0%	0
7-12 hours	12%	5	0%	0	20%	1
13-24 hours	2%	1	0%	0	20%	1
1-2 days	7%	3	0%	0	0%	0
3-7 days	5%	2	11%	2	0%	0
Unknown/NA†	46%	19	53%	10	40%	2
TOTAL§	101%	41	102%	19	100%	5

*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame. (For complete definitions of Groups A-D, see pages 17-18.)

†Includes cases for which a discrete ingestion could not be identified.

§Percent (%) may not total 100 due to rounding.

Table 6-8

Time From Last Ingestion Of Implicated Aspartame-Containing Product(s)
To Cessation of Neurological/Behavioral Symptoms
By Reported Symptoms
Group D* Excluded

Time	Insomnia		Mood Alterations†		Fatigue	
	%	No.	%	No.	%	No.
≤ 1 day	5%	1	13%	5	6%	1
2-3 days	25%	5	36%	14	44%	8
3-6 days	15%	3	10%	4	6%	1
7-30 days	20%	4	8%	3	6%	1
Still Symptomatic	5%	1	3%	1	6%	1
Unknown/NA§	30%	6	31%	12	33%	6
TOTAL¶	100%	20	101%	39	101%	18

*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.
(For complete definitions of Groups A-D, see pages 17-18.)

†Includes anxiety, irritation, agitation, and depression

§Includes cases in which this variable was not calculated because a discrete ingestion could be identified.

¶Percent (%) may not total 100 due to rounding.

NEUROLOGICAL/BEHAVIORAL SYMPTOMS: CASE REPORTS

The following case reports represent a sample of the neurological/behavioral complaints that we chose after the reinterviews to illustrate a variety of points about the neurological/behavioral reports. In addition to some Group A case reports, others are presented because the case histories were cogent, they dealt with severe symptomatology, or they served to illustrate the difficulties inherent in evaluating this type of data.

Several of the case reports describe some of the more common symptoms associated with aspartame by the Group A complainants. In this group, headaches were the most frequent, with 11 of the 18 Group A complainants reporting this symptom. Insomnia was the next most frequently reported symptom and was reported by five of these complainants. Mood alterations were reported by four. Case reports are included that illustrate each of these complaints. (See case reports V-0412 and V-0455; see also S-0125 and S-0148 in the section on allergic complaints in this report, and case reports V-0476 and V-0477 in the section on gastrointestinal complaints.)

Several of the case reports presented here come from Group B. These reports were classified in Group B because the complainant rechallenged themselves with only one aspartame-containing product, but since several clear and consistent histories emerged from Group B, some of these reports were also included (see case reports V-0042, V-0051, V-0093, and V-0404).

One report illustrates a unique case history of a child with hyperactivity (case V-0002). This case is of note because the symptoms were apparently confirmed in clinical studies by an objective observer. According to verbal communication with the child's pediatrician, double-blind, observer-validated clinical trials were performed on this child. The results of these trials are pending publication and are not yet available for review. However, it has

been reported verbally by one attending physician that the study confirmed the reports of hyperactivity associated with the child's ingestion of aspartame. (Additional case reports of hyperactivity are those numbered V-0030 and S-0565.)

Other case reports illustrate findings from the reinterviews obtained subsequent to the initial preliminary computer analysis, (e.g., reports of a dose-response effect: cases V-0042 and V-0404). Several others illustrate in greater depth the character of the symptomatology, such as the case reports describing the complainants' headaches as similiar to headaches resulting from monosodium glutamate (MSG) ingestion (case reports V-0093 and V-0404).

Several case reports describe fairly severe symptomatology such as extreme mood alterations (case reports M-0328, T-0346, and V-0415). Several of these reports are of note because of the complex case histories, and illustrate the difficulty involved in attempting to assess the relationship, if any, of the symptoms to the ingestion of aspartame. For example, several of the symptoms experienced by complainants are of such a nature that they could not be assessed by an observer. In one case, a complainant (V-0047--allergy case reports) reports "hallucinating," which he describes as meaning "things not looking normal;" and in two other cases, the complainants report feeling "suicidal" (case reports M-0328 and V-0415). Many of the symptoms occurred over long time spans and therefore involve extensive recall problems. Also, several of the cases have unexplained medical findings such as liver and kidney dysfunction (M-0328) or previous medical histories that are relevant to the complaint, such as whiplash injury in a complainant reporting severe headaches (T-0346). The complexity of these histories precludes any conclusive statements being made about them, but they do serve to illustrate the very intricate nature of many of the neurological/behavioral reports.

V-0002: Neurological/Behavioral, Group A

A 4-year-old white male had symptoms of insomnia, headache, aggressive behavior, and disorientation. His mother reported that he appeared "glassy eyed" and was "running around wildly...hitting his head against the wall," and that his speech was rapid and slurred. The symptoms first occurred while he was consuming 2-3 glasses of Kool Aid® or Wyler's® lemonade daily along with Halfsies® cereal 3 times per week. His symptoms stopped approximately 24 hours after he stopped ingesting these products. Since this time, the child has participated in a double-blind,* videotaped, observer-validated study. This study reportedly confirmed that the symptoms occur following aspartame ingestion. The symptoms have also consistently recurred on at least three occasions when the child was "accidentally" given three different foods with aspartame--hot chocolate, bubble gum, and cookies. The child's private pediatrician, who feels that the child's symptoms are due to aspartame, reported that he has observed that the child's symptoms have become more prolonged with increased exposure to aspartame.

Relevant Medical History: The child's mother reports that he is allergic to milk protein, but that he has no other allergies.

* The report of double-blind trial is based on verbal communication with the investigator. The results are being prepared for publication and are not available for review at the time.of this report.

V-0030: Neurological/Behavioral, Group A

A 7-year-old white male had symptoms of hyperactivity, irritability and agitation, extreme excitability, and insomnia. The parents first noticed symptoms in the child during a one-week period in which he was consuming 1-2 packets per day of the table-top sweetener, Equal®. During this period, the child's first-grade teacher called and asked the parents if he was on any medication because she had noticed that he had become inattentive, very talkative, and overactive. Intake of Equal® was discontinued, and 3 days later, his behavior had returned to normal at school and at home. Seven months later, the symptoms of hyperactivity, agitation, and excitability occurred with greater severity within 1 hour of ingesting another aspartame product (about 1 pint of Kool Aid®). The symptoms lasted about 16 hours and were accompanied by insomnia. The child was not referred to a physician about his symptoms.

Relevant Medical History: The child has had mild to moderate sensorineural hearing loss since birth. He also has had a reaction somewhat similar to the reported symptoms after taking on one occasion the medication Dimetapp® at 18 months of age.

V-0042: Neurological/Behavioral, Group B

A 30-year-old white female reported symptoms of severe headache, disorientation, and loss of depth perception. Her first symptom, which she described as a severe headache, occurred within 45 minutes of her first ingestion of an aspartame product (2 glasses of lemonade-flavored Crystal Light®), and lasted overnight. The next day, she ingested the same amount of this product and again had a similar experience. The following day, she drank several 14 oz. glasses of the product on an empty stomach. Two to 3 hours later, she became disoriented while driving her car and experienced "loss of depth perception," which made it difficult to drive. She also became confused about what street she was on. The disorientation and headache lasted throughout the afternoon (about 3 hours). Several days later she consumed the aspartame product again and had the same reaction. She then recognized a connection between the drink and her symptoms and stopped ingesting the product.

Relevant Medical History: None.

V-0051: Neurological/Behavioral, Group B

A 33-year-old white female reported symptoms of dizziness and lightheadedness, which she described as being similar to symptoms she has experienced after taking cold tablets. Her first symptoms occurred 10-20 minutes after first using an aspartame product (1/2 packet of Equal®) in her coffee. The symptoms "came and went in waves at about 10-20 minute intervals" for 2-5 hours. These symptoms recurred the next day with similar latency and duration after again using the same amount of the aspartame product. The complainant stopped consuming Equal® and no longer had symptoms. She did not see a physician about her symptoms.

Relevant Medical History: The complainant has not been under medical care or used any medications except Contac® in the past 2 years.

V-0090: Neurological/Behavioral, Group A

A 39-year-old white female complained of depression, memory loss, lethargy, irritability, dizziness, and headaches. The complainant's first use of aspartame-containing products was in March, 1983, when she began using approximately 8 packs of Equal® per day. During the symptomatic interval, the complainant added other aspartame-containing products to her diet, including Diet Coke® and Kool Aid®. The symptoms started in mid-April and increased in number and intensity in subsequent months. The first symptom to occur was lethargy. Over the ensuing months, irritability, dizziness, depression, and memory loss occurred. She states that when she stopped using aspartame-containing products in mid-September following a news report, the symptoms improved within 1 day and ceased within 1 week. The complainant subsequently rechallenged herself approximately 2 months later with Equal®, consuming 4 packets per day for approximately 3 days. She stated that she became dizzy on the third day and that the episode was "very frightening." After these symptoms appeared she stated that she stopped consuming Equal®, and approximately 24 hours later the symptoms subsided.

The complainant consulted three physicians during this time. Only her family physician was available for interview, and he stated that he "had no reason to doubt the judgment of the complainant."

Relevant Medical History: The patient has a past history of thyroid disease as well as a past history of migraine headaches for which she was on Valium® and Cafergot® at the time of the symptoms. Thyroid screen at the time of the symptoms was reported to be normal. The only other medical condition reported was an allergy to ampicillin and compazine.

V-0093: Neurological/Behavioral, Group B

A 39-year-old white female reported symptoms of nausea, headache, and dizziness. The headache and dizziness occurred 1 hour after her first ingestion of an aspartame-sweetened Sprite® and lasted 6 hours, while the nausea occurred about an hour and a half after ingestion. These symptoms recurred the next day after again drinking this product, though the time frames reported for this second episode were somewhat shorter than for the first. Ten to 15 minutes after ingesting the product, she experienced dizziness. Forty minutes after ingestion, she experienced a headache and nausea. All of the symptoms lasted 12 hours. The complainant no longer consumes aspartame products. She did not see a physician about her symptoms.

Relevant Medical History: The complainant has a history of migraine headaches. She reported that her response to this aspartame product was identical to symptoms she has had after eating foods that contain monosodium glutamate.

M-0328: Neurological/Behavioral, Group C

A 17-year-old white female reported symptoms of lethargy, depression, severe mood swings, and suicidal tendencies. (The parents of the complainant were interviewed because they did not wish their daughter to be subjected to the stress of talking to the investigator.) They reported that the symptoms began within 2 weeks of first regular use of a product containing aspartame. (At a different interview, the complainant's parents reported that she used one-half packet of Equal® per day for approximately 2 months prior to the first recorded symptoms.) The complainant's parents also reported that, during the symptomatic period, the complainant consumed eight 12-ounce cans of Diet Coke® per day, one-half packet of Equal® per day, two quarts of Crystal Light® drink per day, and one quart of Crystal Light® iced tea per week.

The parents described their daughter previous to the symptomatic episode as "healthy, vibrant, and positively motivated, with a genius I.Q. in excess of 170." They stated that she was a "straight-A" student who was very athletic and always "diet conscious" and that artificially sweetened drinks were the only "non-nutritious" foods that she ingested.

The parents described the complainant during the symptomatic episode as a "weak, fragile, depressed person who has lost her sense of independence and her spirit." They reported that the complainant was seen by several physicians during her symptomatic episode for uncontrollable mood swings, lethargy, and "plan to commit suicide." In February 1984, an osteopathic physician diagnosed an impairment of liver and kidney function of unknown etiology. The physician treated the complainant with megadoses of vitamins B and C.

(M-0328 continued)

The complainant stopped taking aspartame-containing products in January of 1984. During a follow-up phone conversation, the complainant's mother said that the complainant's condition had improved somewhat, but that her kidney screen has become abnormal again, and that her psychotherapist is considering placing her on antidepressive medication. Although the complainant has not used aspartame for almost 9 months, her physician said that aspartame was suspect because symptoms coincided with ingestion of aspartame products and he could not determine any other etiology for the liver and kidney impairment.

Relevant Medical History: Past medical history is unremarkable with the exception of an allergy to penicillin and a low-calorie diet at the time of the symptoms.

T-0346: Neurological/Behavioral, Group A

The complainant is a 17-year-old white female whose chief complaints were headache, nasal discharge, and mood alterations. The complainant began consuming three packets of Equal® every day in October 1982. The first symptoms occurred within a week of the first use of aspartame-containing products. She states that within 40 minutes of ingestion of the product, she suffered from severe headaches. These headaches were described as being so severe that they "made her mad."

The complainant's mother stated that the headaches became increasingly disruptive and painful until the family, in December of 1982, finally had the daughter committed after she threatened the family members with violence. During her hospitalization, the complainant's mother stated that the complainant did not use any aspartame-containing products and did not suffer from headaches. For the 6 months following her discharge from the hospital, the complainant resumed her use of aspartame and suffered from "fairly mild" headaches. In the summer of 1983, however, the complainant began consuming approximately 6 cans per day of diet drinks and the headaches became increasingly severe. In September of 1983, the patient had a very severe headache and was evaluated in the emergency room where she had an EEG. Results of the EEG were abnormal.

In December of 1983, the complainant saw a news report on television describing symptoms associated with aspartame use. The complainant stated that as soon as she stopped consuming aspartame, the symptoms ceased. She stated that there has been no recurrence of her symptoms since that time with the exception of two episodes in which she "absent-mindedly" forgot about her problems with aspartame and drank a can of diet soda. During both these

(T-0346 continued)

times, the headaches returned. The complainant's mother also indicated that the complainant had had another symptom-free interval around October/November of 1983 when her daughter stopped ingesting Equal® and diet sodas.

According to a verbal report by complainant's physician, it is possible that the complainant has "allergic rhinitis" related to aspartame use, but he stated that there is no way to test or prove this and that he is not positive of the diagnosis. The mother also stated that she is unsure whether her daughter's symptoms are due to aspartame or due to an automobile accident that occurred in June of 1982 in which the patient suffered a whiplash injury.

Relevant Medical History: Complainant reported whiplash injury, June 1982.

V-0404: Neurological/Behavioral, Group B

A 33-year-old white male physician reported symptoms of a severe, bitemporal vascular headache. His first symptoms occurred about 15 minutes after his first substantial ingestion (16 oz.) of Carnation® hot chocolate.

His symptoms first occurred about 1 month after he began ingesting aspartame products: diet soft drink (Pepsi Free®), hot chocolate (Carnation®), and table-top sweetener (Equal®); however, he reported that he used these products very intermittently and in low quantities.

On the occasion of his first substantial ingestion of Carnation® hot chocolate, the symptoms lasted 3 hours. They recurred the next day when he "experimented" by again drinking 16 oz. of the same product on an empty stomach. The latency and duration of symptoms was the same as the first episode. The complainant reported that his symptoms were dose-related in that he experienced a severe headache with two cups of hot chocolate, a headache of lesser intensity with one cup, and no symptoms with one-half cup of Diet Pepsi ®. The complainant, a staff psychiatrist, did not see a physician about his symptoms.

Relevant Medical History: The complainant has had similar symptoms after ingesting Chinese food containing monosodium glutamate.

V-0412: Neurological/Behavioral, Group A

A 28-year-old white male reported insomnia, which first occurred 4 to 8 hours after his first ingestion of the table-top sweetener, Equal®. The insomnia lasted 8 hours. For four consecutive nights after using Equal®, the insomnia recurred and was of the same latency for onset and duration as the first night. The complainant discontinued use of this product and his normal sleep patterns "immediately" returned. Five months later, the insomnia recurred 4 hours after ingestion of another aspartame-containing product (Diet Pepsi®). The insomnia again lasted 8 hours. The complainant no longer uses aspartame products and no longer has symptoms.

Relevant Medical History: Remarkable only for a history of high blood pressure controlled with Catapres®.

V-0415: Neurological/Behavioral, Group C

A 62-year-old white male reported symptoms of acute depression with thoughts of suicide. These symptoms occurred approximately 10 days after beginning daily ingestion of an aspartame product (table-top sweetener, Equal®). The symptoms continued up until approximately 3 days after he discontinued use of this product. (Complainant was not sure of exact time frames.) He has not consumed this product since and has not had recurrence of symptoms. The complainant did not see a physician about his symptoms and stated that he never experienced these symptoms prior to using this product.

Relevant Medical History: None.

V-0455: Neurological/Behavioral, Group A

A 30-year-old white female reported symptoms of moodiness, insomnia, craving for carbohydrates, and weight gain. The complainant was unsure when her symptoms first occurred, but suspected they began the same season she began using aspartame products. She had been consuming daily three such products (Diet Coke®, Diet 7-Up®, and Kool-Aid ®--2-3 glasses/day) in the fall and another aspartame product (Swiss Miss® hot chocolate--2-3 cups/day) during the winter. In March the complainant "experimented" by stopping and restarting the use of aspartame-containing products. The symptoms of moodiness, insomnia, and craving for carbohydrates recurred about a day after restarting use and lasted for 2 to 3 days. After discontinuing use, she no longer had these symptoms. The complainant did not see a physician about her symptoms.

Relevant Medical History: At the time of symptoms, the complainant was taking Synthroid®.

S-0565: Neurological/Behavioral and Gastrointestinal, Group A

The mother of a 7-year-old white male reported that her son had abdominal pain, headache, fever, and hyperactivity. His first symptoms occurred within 4 hours after consuming Diet Coke®. The symptoms lasted for 12 hours. Approximately 1 week later he was given a Featherweight® dessert mix and had the same symptoms with the same latency and duration. Approximately 1 week after this second incident he consumed Alba® hot chocolate mix and experienced a third, identical episode.

Relevant Medical History: The complainant is under treatment for food allergies (sugar, spinach, fruits) and allergies to dust and molds. Allergy shots are given every 8 weeks.

NEUROLOGICAL/BEHAVIORAL SYMPTOMS: DISCUSSION

One of the most notable findings of this analysis was the number and diversity of symptoms reported. In order to provide a framework for the analysis, we described a wide range of the reported symptoms as neurological/behavioral. Thus this category is a broad one including symptoms as diverse as headaches, insomnia, mood alterations, cognitive and motor disturbances, sensory alterations, and generalized fatigue and weakness.

Because of the multiplicity of symptoms that were initially described, it was necessary to break this category down into specific symptoms or symptom categories (e.g., mood alterations) for the analysis. Following this cataloguing of the neurological/behavioral symptoms, we attempted to screen the wide range of reported symptoms in order to identify any that might be related to aspartame ingestion. One screening mechanism we used to accomplish this was to focus on the most frequently reported symptoms. This procedure highlighted headaches (the most frequently reported single symptom) and mood changes (the most frequently reported symptom category). Dizziness, insomnia, and fatigue were the next most frequently reported single symptoms, each being reported about half as frequently as headaches. Thus, these most frequently reported symptoms were initially considered to have a somewhat greater likelihood of being related to aspartame ingestion than those that were reported quite infrequently (such as loss of sense of smell). Frequency of report, however, could be considered only a preliminary screening mechanism; this criterion is probably influenced by other factors, such as the prevalence of the symptom in the general population, the perceived seriousness of the symptom, and the exposure of complainant to media publicity.

Consistency and plausibility of time-frame data was another criterion used to assess the likelihood that neurological/behavioral symptoms might be

associated with aspartame ingestion. Once again, however, this criterion has important limitations. In general some of the more acute symptoms, such as headaches and dizziness, might be more easily associated by the complainant with a discrete episode of ingestion. Some of the other symptoms, such as fatigue or mood changes, are more diffuse in nature and do not lend themselves as readily to identification with a clear-cut time frame. Thus, information necessary to calculate latency and duration was generally unavailable for the more diffuse symptoms such as fatigue or mood changes. In those cases that had the data, however, the time frame for these symptoms was apparently longer than for the more acute symptoms. If any of these more diffuse symptoms are in fact due to aspartame ingestion, it is not possible to determine from this type of analysis whether we observed longer time frames because symptoms such as fatigue or mood changes require longer periods of ingestion before the symptoms become manifest or because the time of onset is more difficult to identify.

In light of the difficulties associated with the wide range and diffuse nature of many of the neurological/behavioral complaints, classification of cases into Groups A-D with the subsequent intensive follow-up of pertinent case reports became a particularly valuable tool for identifying the reports potentially more likely to be due to ingestion of aspartame-containing products. This procedure gave us several analytic options that were not available through the initial computer analysis. First, the case report format gave us the opportunity to explore variables in depth that were not available in the initial data base. For example, several of the complainants with headaches (V-0042, V-0404) reported a dose-response effect such that lesser doses produced modified or negligible symptoms compared to higher

doses. Case V-0042 reported an additional symptom (visual disorientation) after ingesting greater quantities on an empty stomach. The case report format also permitted us to obtain additional useful information through reinterviews with some of the unique or noteworthy cases. The child with hyperactivity who was involved in the clinical trial (V-0002) is one such particularly interesting case. Unfortunately, this case is the only one that received such intensive scrutiny by objective observers. However, the reported findings in this case are at least sufficient to suggest that further inquiry into hyperactivity may be warranted. The case report format also allowed us to define the nature of the symptoms in greater detail than was possible in the numerically coded, computer analysis phase of the investigation. For example, it is interesting that two of the complainants (V-0093 and V-0404) spontaneously described their headaches as being similiar to those that they have following ingestion of MSG. Finally, review of these cases enabled us to further refine the analytic categories used to categorize the reports.

Due in part to the diverse nature of symptoms reported and the self-selected population of complainants, we could not define a single well delineated constellation of symptoms from the large number of individual symptoms reported. Some of the individual symptoms reported were of note, however, based on our screening criteria. Several of the symptoms, such as hyperactivity and headaches, were of note, based on the cogency of the case reports. Others, such as dizziness and insomnia, were of note based on the relative frequency of report and the consistent nature of the case histories. Interesting as these conjectures are, however, these data are based on reports from individual cases. It would require more definitive methodologies than

were available from this preliminary surveillance system to determine if the association between the reported symptoms and aspartame use is, in fact, a causal one and, if so, what segment of the population of aspartame users might experience symptoms.

COMPLAINTS SUBMITTED AS SEIZURES

Introduction

Complaints containing reports of seizures were evaluated as a separate group, because of their potential severity. The case reports are summarized next, followed by an overall discussion of complaints in this category.

CASE REPORTS: COMPLAINTS SUBMITTED AS SEIZURES

V-0092: Neurological/Behavioral (Seizure-Type Activity) Group C

The complainant, a 37-year-old white male, had been using an aspartame-containing product for 6 months prior to the reported episode. His last ingestion of an aspartame-containing product (Equal®) was reported to be 24 hours prior to the episode. He stated that he was riding a horse, the horse bolted, and he lost consciousness and fell, striking his head. He said that witnesses told him he had a seizure, although the attending physician was not a witness to his seizure. He also stated that he was not under care or hospitalized for any medical problems at the time of the incident or within the past two years, he was on no medications at the time of the incident, and he has no history of seizures.

Call to complainant on August 7, 1984, revealed that he has not used aspartame-containing products since his accident, and that he has had no further symptoms.

Relevant Medical History: No known medical problems.

V-0095: Neurological/Behavioral (Seizure-Type Activity) Group C

The complainant, a 39-year-old white male, started using a product containing aspartame in June of 1982. On June 29, 1983, he reportedly had his first seizure. This was followed by other seizures on October 28, November 11, November 25, November 27, 1983, and January 11 and February 2 of 1984. This person reports drinking an average of 40 cups of coffee per day and has sweetened most of them with Equal®. This person saw a physician on numerous occasions and was hospitalized for his conditions.

Since his first seizure this person has been treated with Triavil®, Dilantin®, Ludiomil®, Tranxene®, Elavil®, Haldol®, Valium®, and Mellaril®. He was diagnosed as having anxiety disorder with panic attacks.

Relevant Medical History: There appears to be the possibility of organic brain syndrome, and the complainant is currently under psychiatric treatment.

V-0097: Neurological/Behavioral (Seizure-Type Activity) Group C

The complainant, a 31-year-old white female, started using aspartame-containing products in May of 1983. She reported that she began sleepwalking in mid-July of that year. On July 28, 1983, she awoke to find herself bruised and sore. According to her physician, the complainant had had an epileptic seizure for which he prescribed Dilantin. Another physician was consulted who agreed with the seizure diagnosis but did not classify it as "epileptic," stating that it may not have been "organic related."

Complainant did not approve release of her medical records to the FDA for review. We recontacted her on August 8, 1984, and learned that she has not used aspartame since the time of her complaint, that she has had no subsequent seizures, and that she is not on any seizure medication.

Relevant Medical History: None.

M-0320: Neurological/Behavioral (Seizure-Type Activity) Group C

The complainant, a 26-year-old white female, had been using aspartame-containing products for approximately 3 months prior to the reported seizure that occurred on January 12, 1984. Within 24 hours prior to the incident, complainant had consumed Equal®, Diet Coke®, and aspartame-sweetened Kool-Aid® and fruit punch.

The complainant was standing at the time of the symptoms, which included a "tingly" feeling, tunnel vision, lightheadedness and seizure. A CAT scan and an EEG performed after the episode were within normal limits. The initial medical diagnosis was orthostatic hypotension associated with inappropriate adrenergic effect and secondary seizure. Another physician was consulted for a second opinion. He indicated that, since the tests were normal, he could not rule out a connection between the use of aspartame and the seizure-type episode, but that he was not familiar with the aspartame issue.

We contacted the complainant by telephone on August 7, 1984, and learned that she has had no further episodes. She has avoided aspartame-containing foods, her weight has been stable, she has not been on any diet plan, and her health has been good.

Relevant Medical History: This person was on a 1000-1200 calorie diet and exercise plan and lost 24 pounds between October 4, 1983, and January 12, 1984.

M-0323: Neurological/Behavioral (Seizure-Type Activity) Group D

The complainant, a two-year-old white female, was first given aspartame-containing products--Equal® on her breakfast cereal and sugar-free Kool-Aid® mix to drink--on January 7, 1983. The date of her first seizure was January 30, 1983. She also had seizures on February 2, 1983, May 25, 1983, and August 8, 1983. The parents reported that not all aspartame ingestions have been associated with seizure activity.

A pediatrician and a neurologist both stated that they did not consider the four seizure episodes to be aspartame-related. Both physicians were unsure of etiology, but each suggested that the convulsions were a common variety of "febrile seizures." They prescribed phenobarbital elixir.

We contacted the father on August 7, 1984, and learned that she has had no further seizures while on phenobarbital, that she has had no further exposure to aspartame, and that her health and her growth and development are normal.

Relevant Medical History: None.

M-0330: Neurological/Behavioral (Seizure-Type Activity) Group D

The complainant, a two-year-old white male, was given an aspartame-containing product on December 13, 1983, and 30 minutes after ingestion, had a grand mal seizure. Similar incidents occurred on December 24, 1983, and January 4, 1984. The child was hospitalized December 13-14, 1983, and given phenobarbital. His physician stated that the first seizure appeared to be a febrile seizure, and the subsequent ones have been typical of epilepsy.

Relevant Medical History: None known.

T-0350: Neurological/Behavioral (Seizure-Type Activity) Group A

The complainant, a 37-year-old white female, first used an aspartame-containing product in January of 1984. Within 24 hours she experienced "an aura of familiarity, anxiety, and nausea." During the week of January 15-21, 1984, she drank four more Diet Cokes®, and each time she had the same experience. She did not see a physician for the reported incidents.

During a follow-up call, the complainant said that she has avoided aspartame-containing products and has not had seizures, with the exception of one time early in July when she inadvertently drank three-fourths of a can of Diet 7-Up containing aspartame. Twenty-six hours after drinking the 7-Up, she had the same symptoms in mild form. She believes aspartame acts as a trigger for her symptoms and that possibly other similar compounds have acted as triggers in the past when she had similar symptoms unrelated to aspartame.

Relevant Medical History: She was diagnosed at age 19 as having jacksonian seizures, but has had little medical follow-up since that time. Complainant reports that she has averaged about two symptom episodes, which were similar in character, per year since age 19. She has been on no medication for her condition.

V-0458: Neurological/Behavioral (Seizure-Type Activity) Group C

The complainant is a 33-year-old white female who first used an aspartame-containing product in June or July of 1983. Approximately 3 months later, on October 9, 1983, the complainant experienced a seizure. Four months later, on February 9, 1984, she experienced another seizure, following which she stopped using Equal®. Her physician's diagnosis was idiopathic epilepsy. He did not know if it was related to aspartame use. Prior to this, complainant reported that she was not under a physician's care nor hospitalized within the past 2 years.

Since the reported episodes the complainant has not used aspartame-containing products, has been in good health, and has remained symptom-free.

Relevant Medical History: None.

S-0558: Neurological/Behavioral (Seizure-Type Activity) Group D

The complainant, a 32-year-old white female, reported that her first regular use of an aspartame-containing product was in June of 1983, 6 months prior to her first symptom episode. In the 24 hours before the reported incident, she consumed 32 oz. of Kool Aid® with aspartame and 24 oz. of Diet Coke®. She reported that her symptoms included headache, neck pain, nausea, dizziness, and a "movement disorder" of her right arm. The medical record from her neurology consultation indicated a diagnosis of "myoclonus without stereotypic pattern," which could have been associated with a functional disorder as well as "true neurologic disease." The physician did not know if the symptoms were related to aspartame use. Complainant did not report similar symptoms after consuming an aspartame-containing product at any other time.

Relevant Medical History: At the time of the incident, complainant was under treatment for hypertension with Minipress®. She reported being on an extremely low calorie diet and had lost 60 pounds in six months. At the time of her episode, she had completed a 4-day fast followed by drinking alcohol with her friends and taking Norgesic® and Darvocet® in addition to Minipress®. She was not able to be reached for follow-up information.

DISCUSSION: COMPLAINTS SUBMITTED AS SEIZURES

As can be seen from the preceding case reports, the nine seizure case reports vary markedly with regard to history and presentation. Two of the reports fell into Group D because physicians attributed the seizure activity to other etiologies (M-0323, M-0330). Another was classified in Group D (S-0558) because the complainant continued to use aspartame without further seizure activity. One report met the criteria of Group A (T-0350), but it is not clear from the history that the symptoms reported constituted true seizure activity. (The symptoms described were "an aura of familiarity, anxiety, and nausea.") Also, this complainant did not seek medical attention, so there is no verification of the diagnosis of seizures.

The remainder of the case reports were classified as belonging to Group C; the majority of these cases reported chronic ingestion of aspartame-containing products with intermittent seizure activity. Among these cases, several histories contained information that suggests plausible alternative etiologies for the seizures, as for example case V-0092, in which the complainant struck his head after falling from a horse, and case M-0320 who had a "secondary seizure" following an episode of orthostatic hypotension while on a low-calorie diet. In some other cases, the complainants described their symptoms as seizures, but the medical record provides other diagnoses; for example, case V-0095 was diagnosed as suffering from "anxiety disorder with panic attacks"; case S-0558 was diagnosed as having a "movement disorder," potentially functional in nature. In two cases (V-0458 and V-0097) there is not a clear alternative explanation for the seizures. In the case of V-0458, a diagnosis of idiopathic epilepsy was made after the complainant experienced two seizures, the first after consuming aspartame for a 3-month

period, and the second 4 months after the first seizure. In this case, since the complainant did not have a seizure until after 3 months of chronic aspartame use, and no history of challenge-rechallenge episodes are available, It is difficult to relate these two seizures to the use of aspartame. In the case of V-0097, the complainant refused to release her medical records, but the history indicates that this complainant also had been using aspartame for at least 2 months prior to the onset of symptoms.

In summary, from the review of the first nine cases containing reports of seizures we could not find convincing evidence that any of the documented seizures had a high probability of being due to ingestion of aspartame-containing products. It is unclear whether the one case that fell into Group A is actually a case of seizure activity, as the history does not fully support this impression and there was no medical diagnosis available. The two cases in which there were no alternative diagnoses or etiology also did not have very convincing time frames regarding to aspartame use and seizure onset, although there may have been a dose effect involved. Seizure activity commonly occurs without a documentable etiology, and this compounds the difficulty of assessing case reports linking aspartame use with seizures. Without benefit of more intensive medical follow-up, we cannot rule out the possibility that aspartame may in some cases act as a trigger for seizure activity, but there is not sufficient evidence from these nine cases to raise our suspicions that this is a likely possibility.

ALLERGIC SYMPTOMS: RESULTS

We have included in this section all rashes and skin eruptions and "sore" throat/mouth regardless of whether or not they were classically allergic-type eruptions.

Demographic Characteristics of Cases

The demographic characteristics of the 40 complainants reporting allergic-type symptoms closely parallel the demographic characteristics of all cases. About half (19) are white females, aged 31-60 years. Ninety-three percent (37) of all cases with allergic symptoms are white; 75 percent (30) are female (Table 7-1). The demographic characteristics of Groups A-C are similar to those of the overall group of subjects with allergic symptoms.

Classification of Cases

Of the 40 cases with allergic symptoms, 18 percent (7) met the criteria for Group A, 15 percent (6) for Group B, 25 percent (10) for Group C, and 43 percent (17) for Group D (Table 7-2). In the discussions that follow Groups A-C only are included.

Description of Symptoms

Of the 23 cases in Groups A-C, 30 percent (7) had symptoms of rash only; 26 percent (6) had rash plus other allergic symptoms such as itching, swelling, and respiratory distress; 26 percent (6) had "sore" throat and/or mouth only; and 17 percent (4) had other allergic symptoms (Table 7-3). Cases with allergic symptoms other than rash had swelling, itching or both. The "sore" throat and/or mouth category included symptoms of a burning sensation, irritation, reddening, or formation of blisters inside the throat or mouth.

Temporal Associations between Symptoms and Use of Aspartame Products

For the purpose of analyzing time intervals, complainants were divided into the following groups: rash and/or itching, "sore" throat and/or mouth, and other allergic symptoms. Unlike other major categories where time intervals were analyzed by complaint, the time intervals in the allergic section are analyzed by complainant. That is, each person was reviewed with regard to the timing of the beginning of his/her symptoms.

Symptom-free Interval: Time from the first regular use of implicated aspartame-containing products to the first allergic symptom(s) (Table 7-4).

The symptom-free interval for over half (12) of the 23 complainants was less than 2 days. The symptom-free interval for 17 percent (4) of these cases (4) was unknown. The range of symptom-free intervals for first allergic symptoms was zero time (immediately) to 12 months. The symptom-free ranges for rash and/or itching, "sore" throat and/or mouth, and other allergic symptoms were 10 minutes to 12 months, immediately to 2 hours, and 1 to 3 days, respectively.

Latency of Onset: Time from most recent ingestion of implicated product to symptoms (Table 7-5).

The latency interval for 73 percent (17) of complainants was less than 13 hours with the latency interval of all but one of the remaining cases being unknown or not applicable (Table 7-5). The range of latency intervals for first allergic symptoms was "immediately" to 2 days. The latency ranges for rash and/or itching, "sore" throat and/or mouth, and other allergic symptoms were 10 minutes to 2 days, immediately to 12 hours, and 2 to 12 hours, respectively.

Duration: Time over which the episode occurred after ingestion of aspartame-containing products (Table 7-6).

Duration of symptoms varied considerably (5 minutes to 1 month) among the 11 cases in which symptom duration is known or applicable (Table 7-6). The range of symptom duration for rash and/or itching and "sore" throat and/or mouth was 1 hour to 1 month and 5 minutes to 3 days, respectively. Symptom duration for the 3 persons with other allergic symptoms was unknown or not applicable.

Among the 4 persons (all complaining of rash or itching) in which a discrete ingestion could not be identified, the interval between last ingestion of aspartame product(s) and cessation of first symptom(s) ranged from 1 to 11 days.

Medical History

About half (11) of these complainants reported a history of allergies; over one-third (8), food allergies.

One of the complainants had an illness that may be relevant to occurrence of symptoms. For 15 years this person has had systemic lupus, which is associated with allergic phenomena, and was taking Prednisone®, Chlorambucil®, and Premarin® at the time of symptoms.

Medications

Seventy-four percent (17) of these persons were taking medications at the time of symptoms; twenty-two percent (5) were taking allergy medications.

Physician Visits

Almost one third (7) of these persons saw a physician about their symptoms. Of these, one physician thought that the symptoms were related to aspartame use; two physicians thought that the symptoms might be related to aspartame use.

ALLERGIC SYMPTOMS: TABLES

Table 7-1

Age, Race, and Sex Distribution of Cases
With Allergic Symptoms
By Screening Classification

	All Cases Selected for Review		Group D* Excluded	
	%	No.	%	No.
Age (Years)				
≤20	10%	4	13%	3
21-30	15%	6	13%	3
31-40	23%	9	30%	7
41-50	25%	10	22%	5
51-60	13%	5	0%	0
61+	15%	6	22%	5
Refused/Unknown	0%	0	0%	0
TOTAL	101%	40	100%	23
Race				
White	93%	37	100%	23
All Other	3%	1	0%	0
Unknown	5%	2	0%	0
TOTAL	101%	40	100%	23
Sex				
Male	25%	10	26%	6
Female	75%	30	74%	17
TOTAL	100%	40	100%	23

*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.
(For complete definitions of Groups A-D, see pages 17-18.)

Table 7-2

Distribution of Cases With Allergic Symptoms
By Screening Classification*

	Cases Selected for Review	
	Percent	Number
Group A	18%	7
Group B	15%	6
Group C	25%	10
Group D	43%	17
TOTAL†	101%	40

*Screening classifications:

Group A: Symptoms recurred on rechallenge with more than one aspartame-containing product.

Group B: Symptoms recurred on rechallenge with same aspartame-containing product.

Group C: Symptoms occurred associated with aspartame-containing product, but there was no rechallenge.

Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.

(For complete definitions of Groups A-D, see pages 17-18.)

†Percent (%) may not total 100 due to rounding.

Table 7-3

Distribution of Allergic Symptoms
By Subcategory*
Group D† Excluded

Symptoms	Percent	Number
Rash	30%	7
Rash and other allergic symptoms	26%	6
"Sore" throat/mouth only	26%	6
Other allergic symptoms	17%	4
TOTAL COMPLAINANTS§	99%	23

*By symptom

†*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame. (For complete definitions of Groups A-D, see pages 17-18.)

§Percent (%) may not total 100 due to rounding.

Table 7-4

Symptom-Free Interval
Time From First Regular Use Of Implicated Aspartame-Containing Product(s)
To First Allergic Symptoms*
Group D† Excluded

Time	Rash/Itching %	Rash/Itching No.	"Sore" Throat/Mouth %	"Sore" Throat/Mouth No.	Other Allergic Symptoms %	Other Allergic Symptoms No.
≤ 1 day	47%	7	80%	4	33%	1
2-3 days	0%	0	0%	0	33%	1
4-7 days	13%	2	0%	0	0%	0
8-30 days	7%	1	0%	0	0%	0
1-2 months	13%	2	0%	0	0%	0
>2 months	7%	1	0%	0	0%	0
Unknown	13%	2	20%	1	33%	1
TOTAL§	100%	15	100%	5	99%	3
RANGE =	10 minutes to 12 months		Immediate to 2 hours		1 day to 3 days	

*Figures represent the percent and number of complainants within each time interval.

†Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.
(For complete definitions of Groups A-D, see pages 17-18.)

§Percent (%) may not total 100 due to rounding.

Table 7-5

Latency Interval for First Allergic Symptoms Associated with a Discrete Ingestion of Aspartame-Containing Products* Group D† Excluded

Time	Rash/Itching %	Rash/Itching No.	"Sore" Throat/Mouth %	"Sore" Throat/Mouth No.	Other Allergic Symptoms %	Other Allergic Symptoms No.
≤ 1 hour	27%	4	60%	3	0%	0
2-6 hours	7%	1	20%	1	33%	1
7-12 hours	27%	4	20%	1	67%	2
13-23 hours	0%	0	0%	0	0%	0
1-2 days	7%	1	0%	0	0%	0
>2 days	0%	0	0%	0	0%	0
Unknown/ not applicable§	33%	5	0%	0	0%	0
TOTAL¶	101%	15	100%	5	100%	3
RANGE =	10 minutes to 2 days		Immediate to 12 hours		2 hours to 12 hours	

*Figures represent the percent and number of complainants within each time interval.

†Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame. (For complete definitions of Groups A-D, see pages 17-18.)

§Includes cases for which a discrete ingestion could not be identified.

¶[illegible] may not total 100 due to rounding.

Table 7-6

Duration of First Allergic Symptoms Associated with a Discrete Ingestion of Aspartame-Containing Products* Group D* Excluded†

Time	Rash/Itching %	Rash/Itching No.	"Sore" Throat/Mouth %	"Sore" Throat/Mouth No.	Other Allergic %	Other Allergic No.
≤ 1 hour	7%	1	20%	1	0%	0
2-6 hours	13%	2	0%	0	0%	0
7-12 hours	7%	1	20%	1	0%	0
13-71 hours	7%	1	20%	1	0%	0
3-7 days	0%	0	20%	1	0%	0
> 7 days	13%	2	0%	0	0%	0
Unknown/ not applicable§	53%	8	20%	1	100%	3
TOTAL	100%	15	100%	5	100%	3
RANGE =	1 hour to 1 month		5 minutes to 3 days		N/A	

*Figures represent the percent and number of complainants within each time interval.

†Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame. (For complete definitions of Groups A-D, see pages 17-18.)

§Includes cases for which a discrete ingestion could not be identified.

CASE REPORTS: ALLERGIC SYMPTOMS

All of the cases in Group A were contacted for follow-up interviews. Of these, one no longer felt that symptoms were due to aspartame and withdrew her complaint, leaving seven Group A cases. In three cases, there were minor discrepancies in reporting of symptom time frames. A dose-response relationship between aspartame product consumption and allergic-type symptoms is a possibility with two cases. One complainant had symptoms when she consumed large quantities of two aspartame products, but did not have symptoms when she consumed small quantities of a third aspartame product (case S-0125). Another complainant thought that her symptoms might have been associated with aspartame product "build-up" over several days as well as to the amount of product ingestion on any given day (case S-0148).

Of the seven Group A cases, three had allergic symptoms only. The remaining four had various combinations of allergy plus either neurological/ behavioral or gastrointestinal symptoms on the initial episode. One complainant (V-0047) who initially reported burning and tingling in the mouth with various neurological/behavioral symptoms (feeling "strange," "tense," "uneasy," etc.) experienced only burning and tingling subsequently. In one other case (S-0148), rash and headache occurred on initial ingestion, and headache only on subsequent ingestion.

V-0047: Allergic and Neurological/Behavioral, Group A

A 62-year-old white male reported symptoms of burning and tingling inside the mouth and throat after ingestion of aspartame products on several occasions. In addition, the complainant reported "possible hallucinations" (described as "things not looking right"); and feeling "strange, tense, and uneasy;" and that "something was wrong" after ingestion of an aspartame-containing product. (Note: He did not report the "hallucinations" on reinterview.) His first symptoms occurred about 2 hours after his first and most recent ingestion of an aspartame product (Kool Aid®). The symptoms lasted 8 to 24 hours. (He reported 24 hours in a first interview, and about 8 hours in follow-up interview.) Several months later, similar mouth and throat symptoms occurred and have recurred on occasion after ingesting Carnation Sugar Free Hot Cocoa Mix®. In these episodes, the latency for onset of symptoms was 30 minutes to 2 hours, and the duration of symptoms was 1-2 hours. The complainant still consumes small quantities of aspartame-containing products (e.g., 6-12 oz.. diet soft drink) on occasion, at which time he may experience "very slight burning" inside the mouth. The complainant saw a physician about his symptoms. The physician found the complainant normal except for slight hypertension.

Relevant Medical History: None.

S-0125: Allergic and Neurological/Behavioral, Group A

A 33-year-old white female reported symptoms of rash, itching, respiratory distress, insomnia, and nightmares. Her first symptoms occurred about 2 weeks after her first ingestion of aspartame-containing products (Wyler's® lemonade; and Kool Aid®) and 2-12 hours after her most recent ingestion of 1 or more of these products. (She reported 12 hours in a first interview, 2 hours in a follow-up interview.) She continued to consume large quantities of these products (a total of 1-2 quarts a day) intermittently for about 2 weeks and observed an increased allergic response with continued product use. During this time, her symptoms recurred after ingesting each of these products on separate occasions; however, she could not recall the number of episodes. Since this time, she has on occasion consumed smaller quantities of diet soft drinks with aspartame (1 12-oz. can in a day) and has not had symptoms. She did not see a physician about her symptoms.

Relevant Medical History: The complainant is allergic to penicillin and sulfa drugs. For 15 years she has had systemic lupus, which is associated with allergic phenomena. She was taking Prednisone®, Chlorambucil®, and Premarin® at the time of symptoms.

S-0148: Allergic and Neurological/Behavioral, Group A

A 34-year-old white female reported symptoms of headache, nausea, and rash. Her first symptoms occurred about 2-4 weeks after her first ingestion of aspartame products (Equal® table-top sweetener, Lipton® iced tea, Alba® milk/water additive; '77 Fit 'n Frosty® drink mix). During this time, she may have consumed one to two servings of all three products on a given day. She estimated that the latency for onset of all symptoms was about one-half hour, but she was not sure. All three symptoms occurred simultaneously. The headaches and nausea lasted about 3 hours. Two months later, headache and nausea symptoms recurred on two separate occasions after ingesting another aspartame-containing product (diet soft drink). She had been consuming the this product for about 4 days prior to experiencing the two symptoms again. The latency for onset of both symptoms and the duration of symptoms were similar to the first episode. The complainant reported that since this time she has consumed about once every 3 weeks over a 3-4 month period 8 oz. of an aspartame product such as a soft drink, and she has not had symptoms. The complainant thinks that her symptoms may be due to aspartame, but that symptom occurrence may be associated with product "build-up" over several days as well as to the amount of product ingestion on any given day.

Relevant Medical History: The complainant has numerous allergies to foods and pollen. Headaches are a common symptom of these allergies; rash is not. The complainant reported she has experienced headaches and nausea after using aspartame products even after consciously trying to eliminate other allergenic substances from her diet and environment.

S-0155: Allergic-Type Symptoms, Group A

A 30-year-old female woman reported symptoms of a reddish rash with whiteheads and itching on her face and chest. Her first symptoms occurred 7-8 hours after her first ingestion of an aspartame product (Crystal Light® powdered drink mix). The symptoms lasted 2-3 days.

Similar but more pronounced symptoms occurred about 1 month later when she drank Lipton® ice tea with aspartame. The latency for symptom onset and duration of symptoms for these episodes were similar to the first episode. She did not see a physician about her symptoms.

Relevant Medical History: The complainant develops acne when she eats dairy products or chocolate.

S-0179: Allergic-Type Symptoms, Group A

A 45-year-old white female reported symptoms of swelling, redness, and itching of the skin around the eyes. Her first symptoms occurred within 1 month (exact time unknown) of her first ingestion of an aspartame-containing product (Equal®). The symptoms gradually became worse during the 6-8 weeks she used the product, but subsided when she stopped using the product. Similar symptoms occurred on at least one rechallenge with a different aspartame-containing product (Diet Coke®) several weeks or months after the first long episode. The latency for symptom onset was 15-30 minutes, and the duration of symptoms was 2-3 hours. The complainant now tries to avoid aspartame-containing products, but on occasion still consumes them (about once a month), at which time her symptoms recur. She did not see a physician about her symptoms.

Relevant Medical History: The complainant develops "watery eyes and upper respiratory congestion" when she eats cheese, and she may also experience symptoms after ingesting milk. She may have been taking an antihistamine at the time of the first episode.

V-0461: Allergic-Type Symptoms, Group A

A 42-year-old white female reported symptoms of reddening of the mouth with small blisters forming in the margin of the tongue. Her first symptoms occurred within 1 month (exact time unknown) of first ingesting products containing aspartame (Carnation® hot chocolate and Diet Coke®) and about 12 hours after her most recent ingestion of one or a combination of these products. The symptoms lasted 3-4 days. These symptoms recurred on four rechallenges with aspartame products, at least one of these in which a different product (table-top sweetener) was consumed. The latency for symptom onset and duration of symptoms for these subsequent episodes were the same as for the first episode. She did not see a physician about her symptoms.

Relevant Medical History: In the past, the complainant has had "canker sores" in the mouth following an illness such as the flu or a cold and also as a teenager after she chewed bubble gum.

V-0595: Allergic and Gastrointestinal, Group A

A 35-year-old white female reported symptoms of hives and nausea. Her first symptoms of hives and nausea occurred several minutes after her first ingestion of an aspartame-containing product (Diet Coke®). Both symptoms lasted 1-12 hours. (She reported 12 hours in a first interview; 1 hour in a follow-up interview.) The same symptoms occurred the next day when she consumed a different aspartame product (hot chocolate--Swiss Miss Lite®). The latency for symptom onset and the duration of symptoms were similar to the first episode. She did not see a physician.

Relevant Medical History: The complainant has a history of allergies to foods and drugs.

Other Cases of Note (Groups B and C)

One Group B case is a breast-fed infant who, on two occasions, developed a rash that coincided with his mother's ingestion of aspartame-containing products. She ingested Equal® and Crystal Light® drink on one occasion; and one of these products, Equal®, on another occasion.

ALLERGIC SYMPTOMS: DISCUSSION

The allergic category included a range of symptoms that were thought most likely to be allergic: itching, rash, "sore" throat/mouth. Since allergies can be caused by almost any substance in sensitive individuals, it is biologically plausible that either aspartame or one of its metabolites may cause allergies. However, aspartame cannot be shown as a causal agent without rechallenge studies that control for other factors.

Of the allergy symptom categories, the "sore" throat/mouth is the most diverse and includes symptoms of burning sensation, irritation, reddening, or formation of blisters. More information would be needed to determine whether or not the "sore" throat/mouth category represents a reaction to aspartame and, if so, if it represents an allergic phenomenon.

GASTROINTESTINAL SYMPTOMS: RESULTS

Demographic Characteristics of Complainants

The demographic characteristics of the 51 complainants with gastrointestinal (GI) symptoms are similar to the characteristics of all persons reporting symptoms. Approximately half (28) are white women, aged 31-60 years. Ninety-four percent (48) of all GI cases are white; 77 percent (39) are female (Table 8-1). The demographic characteristics of Groups A-C are similar to the overall group of individuals with GI symptoms.

Classification of Cases

Of the 51 cases with GI symptoms, 14 percent (7) met the criteria for Group A, 18 percent (9) for Group B, 37 percent (19) for Group C, and 31 percent (16) for Group D (Table 8-2). For the following sections, only Groups A-C are discussed.

Description of Symptoms

The most common GI symptoms are abdominal pain, 29 percent (16); nausea, 27 percent (15); diarrhea, 20 percent (11), and vomiting, 14 percent (8) (Table 8-3). Nine percent (5) of cases exhibited other types of GI disturbances (indigestion, gas, gastritis, green stools, rectal bleeding).

Time-Frame Information

Symptom-free Interval: Time from first ingestion of the implicated product to first symptoms.

Approximately 60 percent of all GI symptoms were experienced within 1 day after first consumption of the implicated aspartame-containing product (Table 8-4). The symptom-free interval was unknown for seven cases. The range for the symptom-free interval was "immediate" to 11 months.

Latency of Onset: Time from most recent ingestion of the implicated product to symptoms.

The latency interval was less than or equal to 24 hours for all symptoms with a known latency interval (Table 8-5). The latency interval was unknown for three symptoms. The latency interval was within 1 hour of ingestion for 43 percent of abdominal pain symptoms, 54 percent of nausea, 27 percent of diarrhea, and 49 percent of vomiting. The other GI symptoms had a latency between 4.5 and 24 hours. The range for latency of symptoms was from 10 minutes to 24 hours.

Duration: Time over which the symptom episode occurred after discrete ingestion of aspartame-containing products.

For cases with a known duration, most symptoms lasted less than 12 hours: abdominal pain (55 percent), nausea (60 percent), diarrhea (54 percent), vomiting (89 percent) and other GI (40 percent) (Table 8-6). The ranges for each of the symptom categories are: abdominal pain, 30 minutes to 3 days; nausea, 1 hour to 2 days; diarrhea, 30 minutes to 13 hours; vomiting, 3 minutes to 12 hours, and other GI symptoms, 2 hours to 30 hours. Ingestion of aspartame overlapped with symptom episode, and duration could not be calculated for 6 of the 35 cases. In these cases, the time from the last ingestion to last symptoms ranged from from 1 day for abdominal pain to 14 days for rectal bleeding with mucous discharge.

Medical History

Of the 35 complainants, 8 reported no previous medical problems; 7 reported a previous GI problem; two reported a cholecystectomy within the past year. The remaining five cases reported irritable bowel syndrome, ulcer, hiatal hernia, "upset stomach" and "stomach ailment. Other pertinent medical

histories included arthritis (2), alcoholism (1), hypertension (4), diabetes (4), lactose intolerance (1).

Medication History

Of the 35 complainants, 51 percent (18) reported that they were not on medications at the time of symptoms. Two reported using medications for GI problems, and the remaining reported taking a variety of other medications.

Physician Visits

Eighteen percent (6) of complainants reported visiting a physician. Out of the six cases, two physicians thought aspartame may be related to the symptoms, two did not know whether or not the symptoms were related to aspartame use, and two could not be contacted. (In one case the patient would not sign a medical release form; in the other case the physician could not be located for the interview.)

Symptoms in Other Family Members

Thirty-one percent (11) reported similar symptoms in other family members after using aspartame-containing products. Of these, two are included as separate case reports (V-0476, V-0477). Two complainants reported that other family members who did not use aspartame-containing products had similar symptoms. (In one case, symptoms were attributed to allergy to eggs and milk products; and in another case, to a medication allergy).

Table 8-1

Age, Race, and Sex Distribution of Cases
With Gastrointestinal Symptoms
By Screening Classification

	All Cases Selected For Review		Group D* Excluded	
	%	No.	%	No.
Age (Years)				
≤20	12%	6	11%	4
21-30	21%	11	17%	6
31-40	21%	11	26%	9
41-50	20%	10	20%	7
51-60	14%	7	17%	6
61+	10%	5	6%	2
Refused/Unknown	2%	1	3%	1
TOTAL	100%	51	100%	35
Race				
White	94%	48	91%	32
All Other	4%	2	6%	2
Unknown	2%	1	3%	1
TOTAL	100%	51	100%	35
Sex				
Male	23%	12	23%	8
Female	77%	39	77%	27
TOTAL	100%	51	100%	35

*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame. (For complete definitions of Groups A-D, see pages 17-18.)

Table 8-2

Distribution of Cases with Gastrointestinal Symptoms
By Screening Classification*

	Cases Selected for Review	
	Percent	Number
Group A	14%	7
Group B	18%	9
Group C	37%	19
Group D	31%	16
TOTAL	100%	51

*Screening classifications:

Group A: Symptoms recurred on rechallenge with more than one aspartame-containing product.

Group B: Symptoms recurred on rechallenge with same aspartame-containing product.

Group C: Symptoms occurred associated with aspartame-containing product, but there was no rechallenge.

Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.

(For complete definitions of Groups A-D, see pages 17-18.)

Table 8-3

Distribution of Gastrointestinal Symptoms
By Subcategory*
Group D† Excluded

Symptoms	Percent	Number
Abdominal Pain	29%	16
Nausea	27%	15
Diarrhea	20%	11
Vomiting	14%	8
Other GI Symptoms	9%	5
TOTAL SYMPTOMS§	99%	55
Total Complainants		35

*By symptom

†Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame.
(For complete definitions of Groups A-D, see pages 17-18.)

§Percent (%) may not total 100 due to rounding.

Table 8-4

Symptom-free Interval
Time From First Regular Use Of Implicated Aspartame-Containing Product(s)
To Gastrointestinal Symptoms
By Reported Symptoms
Group D* Excluded

Time	Abdominal Pain		Nausea		Diarrhea		Vomiting		Other GI Symptoms	
	%	No.	%	No.	%	No.	%	No.	%	No.
Immediately	--%	--	7%	1	--%	--	13%	1	--%	--
1 day	56%	9	53%	8	64%	7	62%	5	60%	3
2-6 days	6%	1	--%	--	--%	--	--%	--	--%	--
7-29 days	13%	2	7%	1	9%	1	13%	1	40%	2
1-2 months	13%	2	--%	--	--%	--	--%	--	--%	--
2 months	6%	1	13%	2	9%	1	--%	--	--%	--
Unknown	6%	1	20%	3	18%	2	13%	1	--%	--
TOTAL†	100%	16	100%	15	100%	11	101%	8	100%	5
RANGE =	1 day to 3 months		Immediately to 11 months		1 day to 6 months		Immediately to 8 days		1 day to 14 days	

*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame. (For complete definitions of Groups A-D, see pages 17-18.)

†Percent (%) may not total 100 due to rounding.

Table 8-5

Latency Interval for Gastrointestinal Symptoms
Associated with Discrete Ingestion of Aspartame-Containing Products
By Reported Symptoms
Group D* Excluded

Time	Abdominal Pain %	Abdominal Pain No.	Nausea %	Nausea No.	Diarrhea %	Diarrhea No.	Vomiting %	Vomiting No.	Other GI Symptoms %	Other GI Symptoms No.
Immediately	12%	2	7%	1	--%	--%	13%	1	--%	--
4-30 minutes	6%	1	27%	4	9%	1	36%	3	--%	--
31 min.-1 hour	25%	4	20%	3	18%	2	--%	--	--%	--
2-3 hours	12%	2	27%	4	18%	2	25%	2	--%	--
4-6 hours	19%	3	13%	2	36%	4	13%	1	20%	1
7-12 hours†	12%	2	7%	1	18%	2	13%	1	20%	1
13-24 hours	6%	1	--%	--	--%	--	--%	--	20%	1
Unknown/ Not Applicable§	6%	1	--%	--	--%	--	--%	--	40%	2
TOTAL¶	98%	16	101%	15	99%	11	98%	8	100%	5
RANGE =	Immediately to 24 hours		10 minutes to 10 hours		30 minutes to 12 hours		Immediately to 12 hours		4.5 hours to 24 hours	

*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame. (For complete definitions of Groups A-D, see pages 17-18.)

†"Overnight" = 12 hours.

§Includes cases where a discrete ingestion could not be identified.

¶Percent (%) may not total 100 due to rounding.

Table 8-6

Duration of Gastrointestinal Symptoms
Associated with Discrete Ingestion of Aspartame-Containing Products
By Reported Symptoms
Group D* Excluded

Time	Abdominal Pain %	Abdominal Pain No.	Nausea %	Nausea No.	Diarrhea %	Diarrhea No.	Vomiting %	Vomiting No.	Other GI Symptoms %	Other GI Symptoms No.
Immediately	--%	--	--%	--	--%	--	13%	1	--%	--
5-30 minutes	6%	1	--%	--	9%	1	13%	1	--%	--
31 min.-1 hour	6%	1	7%	1	9%	1	--%	--	--%	--
2-3 hours	12%	2	20%	3	9%	1	13%	1	20%	1
4-6 hours	12%	2	13%	2	18%	2	25%	2	--%	--
7-12 hours	19%	3	20%	3	9%	1	25%	2	20%	1
13-24 hours	--%	--	7%	1	9%	1	--%	--	--%	--
1-2 days	12%	2	20%	3	--%	--	--%	--	20%	1
3-7 days	6%	1	--%	--	--%	--	--%	--	--%	--
Unknown/NA†	24%	4	13%	2	36%	4	13%	1	40%	2
TOTAL§	98%	16	100%	15	99%	11	98%	8	100%	5
RANGE =	30 minutes to 3 days		1 hour to 2 days		30 minutes to 13 hours		3 minutes to 12 hours		2 hours to 30 hours	

*Group D: Symptoms did not recur on rechallenge, or physician stated that the symptoms were unlikely to be due to aspartame. (For complete definitions of Groups A-D, see pages 17-18.)

†Includes cases where a discrete ingestion could not be identified.

§Percent (%) may not total 100 due to rounding.

GASTROINTESTINAL SYMPTOMS: CASE REPORTS

For the following case reports, we reinterviewed all complainants classified in Group A. (One case was subsequently withdrawn because on reinterview the complainant attributed symptoms to a "flu".) Of the remaining seven cases, one had gastrointestinal symptoms only, one had abdominal cramps and water retention, four had both gastrointestinal and neurological/ behavioral symptoms, and one had both gastrointestinal and allergic symptoms. There was a possibility of a dose response effect in one case in which symptoms of abdominal cramps and water retention occurred, but not at low doses.

S-0239: Gastrointestinal, Group A

The complainant, a 34-year-old white female, reported symptoms of abdominal pain and gas. Her first symptoms occurred within 2 hours after consuming Equal®, her first use of a product containing aspartame. The symptoms lasted approximately 8 hours. About 3 months after her first episode, she rechallenged herself once with Kool Aid® and once with Crystal Light®. On each occasion she experienced the same symptoms with the same latency and duration.

Relevant Medical History: Complainant has a history of colitis and lactose intolerance.

V-0436: Gastrointestinal and Neurologic/Behavioral, Group A

The complainant, a 47-year-old white male, reported symptoms of nausea, dizziness, and drowsiness. His first symptoms occurred within 30 minutes after consuming Tab®, a diet cola not containing aspartame. The symptoms lasted approximately 6 hours. One month later, all of the symptoms recurred, this time less severely, when he drank Diet Coke®. The latency for these symptoms was the same. The duration for these symptoms was 8-10 hours. Approximately 6 months after this later episode, the complainant reported a slight upset stomach after rechallenge with Diet 7-Up®. The latency for this symptom was 30 minutes and its duration was approximately 1 hour.

Relevant Medical History: The complainant is diabetic, and he regulates his diabetes by his diet. (The complainant is allergic to dust and ragweed, but does not take any allergy medications.)

V-0476: Gastrointestinal and Neurologic/Behavioral, Group A

The complainant, a 27-year-old white female, reported symptoms of cramps, diarrhea, vomiting, and headache. Her first symptoms occurred within 4-5 hours after consuming Diet Coke®, her first use of a product containing aspartame. The symptoms lasted 5-6 hours. Two and one-half weeks later, all of the symptoms except vomiting, recurred on rechallenge with Diet 7-Up®. (Vomiting was reported on re-interview, but not on initial interview.) The latency for symptom onset was the same. The complainant was asymptomatic within 3 days after her last ingestion of aspartame.

Relevant Medical History: The complainant has pollen allergies.

V-0477: Gastrointestinal and Neurologic/Behavioral, Group A

The complainant, a 27-year-old white male (husband of V-0476), reported symptoms of cramps, diarrhea, vomiting, and headache. The symptoms occurred within 4-5 hours after consuming Diet Coke®, his first use of a product containing aspartame. The symptoms lasted approximately 6 hours. Two and one-half weeks later, all of the symptoms except vomiting recurred on rechallenge with Diet 7-UP®. (Vomiting was reported on re-interview, but not on initial interview.) The latency for symptom onset was approximately 12 hours, and the symptoms lasted approximately 8 hours.

Relevant Medical History: The complainant reported two kidney stone episodes, one in December of 1977 and another in September of 1978. At the time of this report, the complainant was taking hydrochlorothiazide for his kidneys.

V-0497: Gastrointestinal Only, Group A

The complainant, a 43-year-old white female, reported symptoms of cramps and retention of body fluids with bloating. Her first symptoms occurred within 12 hours after consuming Diet Coke® and Equal®. The symptoms lasted for 2 days. Approximately 1 month later, the complainant rechallenged herself with Swiss Miss® hot cocoa drink. The latency for symptom onset was the same. The duration of these symptoms was 3-5 days. The complainant stated that these symptoms were related to the amount of aspartame-containing product she ingested because, when she cut back on the volume consumed, her symptoms disappeared.

Relevant Medical History: The complainant reported no medical problems presently or within the past 2 years.

GASTROINTESTINAL SYMPTOMS: DISCUSSION

No clear GI syndrome emerged from the data. Many of the complainants reported a combination of GI symptoms with symptoms from other major categories. Of the 51 cases reviewed with GI symptoms, 31 percent had a history of recurring symptoms on rechallenge with the same or different aspartame-containing products. Several of the complainants had a previous medical history of either GI or other illnesses that would predispose them to GI symptoms. Some even suggested that some of these reported symptoms may have represented either a coincidental exacerbation of a preexisting condition or an increased sensitivity on their part. In addition, several of the complainants reported GI symptoms in other family members who did not consume aspartame-containing products, which suggested the likelihood of other causes of the symptoms.

The difficulty in interpreting the present reported accounts is illustrated by the reinterview findings for Group A case reports. One complainant withdrew her complaint after continuing to use products containing aspartame and no longer having symptoms. A second complainant (V-0436) had repeated GI symptoms (nausea, upset stomach) on ingestion of Diet 7-Up® and Diet Coke®, which both contain aspartame; however, the same complainant reported the most severe symptoms (nausea, dizziness, and drowsiness) on first ingestion of Tab®, a diet cola that did not contain aspartame at the time he drank it. Although this complainant reported repeated symptoms on rechallenge with more than one aspartame-containing product, the similar symptoms he reported on consuming Tab® clearly suggest the possibility of either a placebo effect (the complainant thought that Tab® had contained aspartame) or the possibility that some common factor in cold diet drinks may precipitate GI symptoms in this person.

MENSTRUAL SYMPTOMS: RESULTS

Demographic Characteristics of Cases

All of the 10 women who reported menstrual symptoms were white and ranged in age from 20 to 43. Half (five) were in their twenties, three in their thirties, and two in their forties. The ages of two of these cases who were classified in Group D were 27 and 47.

Classification of Cases

Of the 10 women with menstrual symptoms, none met the criteria for Group A; 2 met the criteria for Group B; and 6 met the criteria for Group C. Two women who reported missed menses were classified into Group D. In one case, her physician did not think her symptoms were related to aspartame. The other had been regularly ingesting large quantities of an aspartame product for some months prior to onset of symptoms. In this case the complainant recalled use of the product prior to aspartame's release on the market. Her symptoms began within a couple of months of having had surgery and the initiation of chemo- and radiation therapy for breast cancer. Because her symptoms appeared to the physicians reviewing this report to be caused by her cancer and the therapy, her case was categorized in Group D. (She refused to sign a medical release to have her physicians contacted.) In the discussions below, only Groups B and C are included.

Description of Symptoms

The menstrual irregularities reported by the eight women in Groups B and C included early (three) and late (two) menses, increased (two) and decreased (two) menstrual flow, clotting (one), spotting between menses (one), and absence of menses (one). Neurological/behavioral symptoms accompanied menstrual irregularities in 75 percent (6) of these women. These symptoms

included irritability (three), headache (two), insomnia (two), loss of concentration (two), fatigue (one), memory loss (one), visual disturbances (one), dizziness (one), and disorientation (one). Other symptoms accompanying menstrual irregularities included urgency to urinate (one) and thirst (one).

Temporal Associations between Symptoms and Aspartame Products

Symptom-free interval: Time from first regular use of aspartame product(s) to menstrual symptom(s).

The date of first menstrual symptoms was calculated as actual or expected date of menstrual period. The symptom-free interval for the 8 complainants ranged from 1-2 days to 7 months, with 6 of the 7 women having symptom-free intervals of less than or equal to 2 months. (One of the seven women indicated use during that "season.") One woman had a symptom-free interval of up to 7 months. This complainant consumed large quantities of an aspartame product during this interval (14 packets of Equal® per day).

Latency and Duration of Symptoms: These time assessments are not applicable, since all complainants continuously rather than discretely ingested aspartame-containing products.

Post Ingestion Symptomatic Interval: Time from the last ingestion of aspartame-containing products to cessation of menstrual symptom(s).

The post-ingestion symptomatic interval for the 8 complainants ranged from 2-3 days to 2-3 months, with all but 1 having post-symptom intervals of less than or equal to 1 month. The remaining woman reported that her menses gradually returned to normal 2-3 months after discontinuation of aspartame-containing products.

All of the five who completely stopped using products containing aspartame reported no recurrence of symptoms. The 3 other women have had, on 1 or more

occasions, not more than 1 12-oz. can of diet soft drink in a day and have not had recurrence of symptoms.

Medical History and Medications Related to Menses

Medical History: Seven of the eight complainants reported that they had not had similar menstrual symptoms before the reported episode(s). The remaining complainant reported similar symptoms about 6 years earlier.

Two of the eight women were on weight-reduction diets at the time of symptoms. One was on a 1000 kcal/day diet for 2-3 months; the other was on a 500 kcal/day diet for 2 weeks. All seven complainants for which weight and height were reported were within acceptable weight ranges at the time of symptoms (1973 Weight Tables, HEW Conference on Obesity).

Medications: Two of the eight complainants were on birth control pills at the time of symptoms. They reportedly take these pills with regularity. One complainant took progesterone around the time of menstrual symptoms in an attempt to relieve neurological/behavioral symptoms that she thought might be related to premenstrual syndrome. Another woman reported that she sometimes takes the pain reliever, Motrin®, for cramps at the start of her menses. She may have been on this medication at the time of symptoms.

Physician Contacts

Only one of the eight women saw a physician about her menstrual symptoms. It is not known whether the physician for this woman thought her symptoms were related to aspartame use, because the physician was unable to be interviewed.

MENSTRUAL SYMPTOMS: CASE REPORTS

All eight women in Groups B and C were contacted for follow-up interviews. Reports follow for seven: two women in Group B, one woman for which a dose effect is reported, and four in which neurological/behavorial symptoms accompanied menstrual symptoms.

T-0345: Menstrual, Group C

A 31-year-old white female reported symptoms of early (1 week) and late (1 week) menses. Her symptoms first occurred about 1 month after starting her heaviest continuous use of aspartame-containing products (diet soft drinks--Diet Coke®, Diet Pepsi®, Sugar Free Sprite®) and about 7-8 months after starting to use other aspartame products (Kool Aid®). She consumed 1-2 glasses of Kool Aid® per day for the first 3 months and then decreased consumption to 1-2 glasses a month for several months. About 1 month before her symptoms started, she began consuming about 4 12-oz. cans of diet soft drink per day, continuing for 4 months. During this time, her menses came early on 2 consecutive months and late on the 3rd month. Her normal menstrual cycle resumed the month after she stopped continuous aspartame product intake and has been normal since. (The complainant reports that she has consumed an occasional diet soft drink since that time without symptoms).

Relevant Medical History: The complainant reported no history of menstrual irregularities of this nature.

M-0357: Menstrual and Neurological/Behavioral, Group C

A 23-year-old white female reported symptoms of absent menses and decreased menstrual flow, headache, fatigue, dizziness, and "feeling bad." Her menstrual and neurological symptoms first occurred about 1 month and 2 weeks, respectively, after first ingesting Diet Rite Cola® containing aspartame. She consumed a total of 2-3 12-oz. cans per day of 3 diet sodas containing aspartame (Diet Rite Cola®, Diet Coke®, Diet Pepsi®) for about 4 months. Her symptom of fatigue was fairly constant. Dizziness would sometimes occur about 1/2 hour after drinking a can of soda. Headaches occurred about every 2-3 days. These neurological symptoms stopped about 1 week after she stopped using aspartame products. Menstrual irregularities occurred for 4 months, stopping about 1 month after she discontinued aspartame ingestion. The complainant reports that since this time she has not consumed aspartame- containing products and has not had these symptoms.

Relevant Medical History: The complainant reported no history of menstrual irregularities of this nature. At the time of symptoms, she had been taking birth control pills regularly for several months.

V-0403: Menstrual and Neurological/Behavioral, Group C

A 20-year-old white female reported symptoms of late menses (1 1/2 weeks), and insomnia. Her insomnia occurred about 5 days after her first ingestion of Kool Aid® containing aspartame. Her menstrual period, expected 1-2 days after starting the aspartame ingestion, arrived 1 1/2 weeks late. She drank 1-3 glasses of Kool Aid® per day for 1-2 weeks. The insomnia continued nightly until 2-3 days after she stopped drinking Kool Aid® intake; the menses arrived about 2-3 days after she stopped drinking Kool Aid®. Since she stopped continuous intake of aspartame-containing products, she has not had symptoms. She recalls consuming an aspartame product (1/4 can of diet soda) on only one occasion since this time.

Relevant Medical History: The complainant reported no history of menstrual irregularities of this magnitude. Prior to this episode, she said she had at most a 2-3 day variance in onset of menses, and that this has since resumed. The complainant reported no history of insomnia and no recurrence of insomnia symptoms since the episode.

V-0420: Menstrual, Group B

A 20-year-old white female reported having symptoms of urgency to urinate and of headache within a few minutes of ingesting an aspartame-containing product, and of early menses (3-5 days). Her symptoms of urgency to urinate and headache* first occurred about 1 month after first ingesting aspartame-containing diet soft drinks--Diet Coke®, Diet Pepsi®, and Diet 7-Up. Her symptoms of early menses occurred about 2 months following her first ingestion of aspartame products. The complainant consumed these products (a total of three 12-oz. cans per day) for about 3 months, with intermittent occurrence ("off and on") of headaches for 1 month and daily occurrence of urinary symptoms. She stopped using aspartame-containing products for 1 month and did not have any of the 3 symptoms. The following month she resumed consumption of these products for a few weeks and again had menstrual and urinary symptoms. She stopped using aspartame products the next 2 months and reported no symptoms during these months. The following month, the complainant consumed 3 12 oz. cans of Diet 7-Up® per day for 2 weeks. The menstrual and urinary symptoms recurred during this time, but stopped after she stopped ingestion of these products. She no longer ingests aspartame.

Relevant Medical History: The complainant reported no history of menstrual irregularities of this nature and no history of urinary tract infection. The complainant often takes Motrin for cramping at the start of her menses.

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* The complainant did not report headache on initial interview; therefore this case report is not included in the neurological/behavioral section.

V-0482: Menstrual, Group B

A 32-year-old white female reported symptoms of increased menstrual flow with large blood clots. Her first symptoms occurred about 20 days after first ingesting aspartame-containing products (Equal® and Kool Aid®). She ingested these products on a daily basis for 4 consecutive months (8 packets of Equal® a day for the first 2 months, decreasing to 2-4 packets per day for the remaining 2 months; 2-3 glasses of Kool Aid® per day for all 4 months). During each of these months, she experienced symptoms. She stopped ingesting aspartame-containing products for about 2 1/2 months, and her menses during this time were normal. She then resumed consumption of 2 packets of Equal® per day for about 1 1/2 weeks and noticed the same symptoms when her menses arrived about 5 days after starting ingestion. The complainant no longer consumes aspartame products and has not had symptoms since.

Relevant Medical History: The complainant reported no history of menstrual irregularities of this nature. The complainant was on a weight reduction diet for 2-3 months, starting at the time of first ingestion of aspartame-containing products, and reported losing 18 lbs. during this period.

V-0495: Menstrual and Neurological/Behavioral, Group C

A 43-year-old white female reported symptoms of decreased menstrual flow of short duration (1 day vs. 4 days), mood changes (e.g., "I would flare up with anger about little things, whereas I am usually laid-back"), and loss of recent memory (e.g., she would forget she called someone a few minutes before and would call the person again). Her symptoms of menstrual irregularity and mood changes first occurred during the same season (exact time unknown) that she began ingesting three aspartame products (Equal®, Kool Aid®, and Diet Coke®). These symptoms came on gradually. Her symptom of recent memory loss first occurred about 4 months after first ingesting these aspartame-containing products and about 1 month after starting to ingest daily a fourth aspartame-containing product (Swiss Miss® hot chocolate). She consumed 1 or more of these daily for about 7 months. Her neurological/ behavioral symptoms occurred almost daily until she stopped ingesting aspartame-containing products, at which time the symptoms gradually faded over a period of a few weeks. Her menstrual symptoms also continued until she stopped aspartame product ingestion, at which time her menses gradually returned to normal over a period of 2-3 months. Since stopping daily ingestion of aspartame products, she has drunk--on about six separate occasions--no more than one can of diet soft drink, and she has not had symptoms.

Relevant Medical History: The complainant reported no history of menstrual irregularities of this nature.

V-0498: Menstrual and Neurological/Behavioral, Group C

A 26-year-old white female reported symptoms of increased menstrual flow of early (1 week) onset, insomnia, irritability, and loss of concentration. Her symptoms first occurred about 1 1/2 months after first ingesting aspartame-containing products (diet soft drinks--Diet Coke® and Diet Rite Cola®; powdered drink mixes--Wyler's® Sugar Free Drink, Kool Aid®; and dessert mix--D-Zerta®). She consumed 2-4 12-oz. cans of diet soft drink per day for 2-3 months in addition to the dessert mix about once a week and powdered drinks about once every 2 weeks. The neurological/behavioral symptoms continued until about 1 week after discontinuing aspartame product use; the menstrual symptoms continued until about 1 month after discontinuing use. Since this time, the complainant has not consumed aspartame-containing products and has not had these symptoms.

Relevant Medical History: The complainant reported no history of menstrual irregularities of this nature. She has taken birth control pills regularly for about 9 years.

MENSTRUAL SYMPTOMS: DISCUSSION

Although menstrual symptoms were reported by relatively few complainants among the first cases received at CDC, (5 percent of 199 complainants), this category is applicable only to a subset of total complainants (i.e. pre-menopausal women). Of the 10 cases with menstrual complaints reviewed here, two of these women were classified into Group D. The third consumed large quantities of aspartame products daily for 5 to 7 months before onset of symptoms and was on a low-calorie weight reduction diet at the time of symptoms. For the remaining seven complainants, the type of menstrual symptoms reported varied considerably, including alterations in expected timing of menses to alterations in expected quantity of menstrual flow.

Time frame information is difficult to assess for menstrual abnormalities because of the inherent temporal nature of the menstrual cycle, but it was established that five of the seven complainants had been consuming one or more aspartame products daily over a period of months before the time symptoms first occurred. Also, recurrence of symptoms was reported to be associated with continuous (daily) ingestion of aspartame product(s) in two cases, but symptoms were not reported to recur in the case of three women who "rechallenged" with one or more discrete ingestions of small amounts of aspartame product(s).

Cases containing reports of menstrual symptoms were screened for alternative explanations for their symptoms, such as low body weight at time of symptoms, improper use of birth control pills, use of other hormonal medication, history of similar menstrual irregularities, etc. Although alternative explanations for the majority of the menstrual complaints were not established, it not was uncommon for women to experience alterations in

menstrual patterns from cycle to cycle without an obvious medical explanation. Additionally, without the benefit of medical examination, a number of alternative explanations for the menstrual complaints might be missed entirely.

The evaluation of menstrual symptoms compared to the other major symptom categories might be expected to be particularly difficult because of a number of factors. The diffuse nature of these symptoms bring to mind spurious associations or, alternatively, might cause any potentially real associations to be overlooked. Menstrual abnormalities frequently are accompanied by little or no pain, discomfort, or inconvenience in contrast to the other symptom categories and therefore might not draw the woman's attention. Finally, many women experience variations in their menstrual cycles without being outside the norm. In the absence of a clear, consistent pattern of report of menstrual disturbance(s), it is not possible to evaluate whether the menstrual cases reviewed here are due to normal menstrual variability, menstrual irregularities due to other causes, or menstrual symptoms in fact associated causally with aspartame ingestion.

SUMMARY AND CONCLUSION

In summary, the quality and type of evidence obtained by a passive surveillance system based on consumer complaints precludes definitive determination of whether these complaints are or are not caused by the agent under question--in this case, aspartame. However, it is possible under these circumstances to provide a basic descriptive analysis and to attempt to identify consistent patterns of report. Analysis of the demographic characteristics of the complainants revealed that the great majority were white women 20-60 years of age. This overrepresentation of women may reflect a greater use of aspartame-containing products, a greater tendency to report their symptoms, or a greater susceptibility to side effects from aspartame. Available data are not adequate to resolve this issue.

A wide variety of symptoms was reported. No specific constellation of symptoms was identified in relation to aspartame ingestion; however, a substantial number (25-30 percent) of individual complainants reported that their symptoms recurred after repeated consumption of aspartame-containing products without evidence of misuse or other alternative explanation. How many of the individuals who reported repeated episodes of symptoms after aspartame use had symptoms that were due to aspartame, we cannot determine. Whether the symptoms experienced by persons who chose not to use aspartame again were caused by aspartame is also not clear. In a few instances persons who had challenged themselves several times with aspartame-containing products found by the time of our reinterview that their symptoms were, in fact, not due to aspartame. These individuals had used aspartame without such symptoms subsequently or had come to alternative explanations for their symptoms.

Thus, this investigation of consumer complaints of symptoms experienced after consumption of aspartame-containing products has identified no specific constellation of symptoms related to aspartame consumption. Nonetheless, some individual symptoms were reported with greater frequency than other symptoms, and 28 percent of individual complainants reported experiencing repeated episodes of symptoms after aspartame use. While some of these reports are undoubtedly due to mere coincidental occurrence of symptoms after aspartame consumption, and others may be due to the suggestibility of some persons, still others may be attributable to some as yet undefined sensitivity to aspartame in commonly consumed amounts. The only way that these possibilities could be thoroughly evaluated would be through focused clinical studies.

APPENDIX

CASES REVIEWED FOR DEMOGRAPHIC AND SYMPTOM-SPECIFIC INFORMATION ONLY

Introduction

The first 231 completed questionnaires received at CDC were coded for intensive computer analysis. The following results are based on the remaining 286 questionnaires, which were coded for demographic and symptom-specific data only, for the purpose of assessing comparability with the first 231.

Consumer complaints originally submitted to the FDA and to G.D. Searle and Company made up the bulk of the cases examined in this report (Appendix Table 5). The FDA received 110 reports; G. D. Searle and Company received 92 reports. Dr. Woodrow C. Monte, Director, Food Science and Nutrition Laboratory, Arizona State University, Tempe, Arizona, provided 50 consumer complaints that had been originally submitted to him. Also included in this group were 31 additional complaints that had been submitted to the State of Arizona. The remaining three reports came from Mr. James C. Turner, Counselor, Community Nutrition Institute, Washington, D.C.

Summary of Results and Discussion

Overall, the demographic distribution of these cases was similar to the first 231 cases reviewed at CDC. Once again, the complainants were predominantly female (76 percent) (Appendix Table 1) and white (97 percent) (Appendix Table 2), with the majority being between the ages of 21 and 60 years (Appendix Table 3).

The distribution of complainant's States of residence did, however, differ from the initial analysis. Reports were again received from many different States; in this case, 23 percent were received from Arizona.

Forty-six percent of these 67 Arizona cases were included in reports that the FDA solicited from Dr. Monte.* The increased number of complaints received from residents of Arizona is most likely attributable to the publicity in Arizona surrounding the concerns raised there by Dr. Monte. It is also likely that many of the other complainants residing in Arizona were aware of Dr. Monte's concerns and were thus encouraged to submit complaints to the FDA, G.D. Searle and Company, or to the Arizona State Health Department.

For both the initial 231 cases and the subsequent 286, there were relatively few cases reported until the summer of 1983 (Appendix Table 6). In the analysis of the first 231 cases, there were fewer reports during the fall of 1983 and then another peak of reports in the winter of 1983-84. In the analysis of the subsequent 286 cases, reporting did not decrease during the fall of 1983, but continued through the winter of 1983-84. This apparent difference in reporting rates in the fall of 1983 is most likely due to the instructions that the field investigators received to concentrate initially on the most recent reports in order to maximize recall by the complainants. According to these instructions, the complaints received in the winter of 1983-84 would have been reinterviewed prior to those in the fall, thus giving the appearance of a lowered reporting during the fall of 1983.

The distribution of symptoms reported between the first 231 cases and the remaining 286 cases was similar (Appendix Table 7). The most frequently reported symptoms were in the neurological/behavioral and GI categories. In the neurological/behavioral category, headaches and mood alterations were

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*(As is noted in Appendix Table 5, 11 percent of the complaints were received from the Arizona State Health Department, a source of report that was not present in the initial 231 cases analyzed.

again the most frequently reported symptoms (Appendix Table 8). In the analysis of the 286 cases, mood alterations were more frequently reported than headaches; but the difference is not large, and mood alterations is a category that includes a number of different symptoms, while headaches is a single symptom.

The GI and allergic symptom categories were reported with similiar frequency in the later analysis, and the distribution of symptoms reported was also similiar to the first 231 (Appendix Tables 9 and 10). Slightly more GI complaints also were accompanied by neurological/behavioral complaints; however, as discussed in the preceding paragraph, the neurological/behavioral complaints did not appear to differ significantly from the initial 231.

One death involving a worker in a G. D. Searle and Company plant was reported to be among the 286 cases. The clinical history has been reviewed by the FDA, and it was not felt that there was any indication that this death was associated with aspartame ingestion. Details are available in the case report V-0656 included in this Appendix on page 145.

Then, a small number of symptoms was reported in the analysis of the 286 cases that were not reported in the earlier analysis; the frequency of such reports, however, was very low (Appendix Table 12). No previously unrecognized category of complaint emerged in the later analysis in sufficient numbers to warrant concern that the initial analysis had not picked up a neurological/behavioral symptom complex present in the total population of complainants. Overall, the demographic characteristics and distribution of symptoms in the 286 cases analyzed in this section of the report were very similar to the initial 231 cases that were analyzed in depth. The comparative review did not indicate any bases for concern that the initial 231 cases were likely to be unrepresentative of the overall group of reported symptoms.

CASES REVIEWED FOR DEMOGRAPHIC INFORMATION: TABLES

Appendix Table 1

Sex Distribution of Remaining Cases

Compared with Initial Cases Selected for In-Depth Review

Sex	Remaining Cases Percent	Cases Selected for Review Percent
Male	24%	25%
Female	76%	75%
TOTAL	100%	100%

Appendix Table 2

Race Distribution of Remaining Cases
Compared with Initial Cases Selected for In-Depth Review

Race	Remaining Cases Percent	Cases Selected for Review Percent
White	97%	94%
All Other	2%	3%
Unknown	1%	3%
TOTAL	100%	100%

Appendix Table 3

Age Distribution of Remaining Cases Compared with Initial Cases Selected for In-Depth Review

Age	Remaining Cases Percent	Cases Selected for Review Percent
≤20	10%	9%
21 - 30	22%	18%
31 - 40	26%	26%
41 - 50	17%	20%
51 - 60	17%	13%
61 +	9%	11%
Unknown	0%	2%
TOTAL*	101%	99%

*Percent (%) may not total 100 due to rounding.

Appendix Table 4

Distribution of Remaining Cases Compared with Initial Cases Selected for In-Depth Review By State of Residence

State	Remaining Cases Percent	Cases Selected for Review Percent
AK	<1%	0%
AL	<1%	1%
AZ	23%	2%
CA	14%	11%
CO	2%	2%
CT	4%	2%
DC	<1%	<1%
DE	<1%	0%
FL	3%	3%
GA	1%	<1%
IL	3%	5%
IN	1%	3%
KS	0%	1%
KY	0%	1%
LA	1%	0%
MA	5%	3%
MD	4%	4%
ME	<1%	0%
MI	2%	6%
MN	1%	1%
MO	<1%	0%
MS	0%	3%
NC	2%	3%
NE	<1%	<1%
NH	0%	1%
NJ	1%	5%
NV	<1%	0%
NY	6%	15%
OH	4%	5%
OK	1%	1%
OR	1%	0%
PA	4%	6%
RI	<1%	<1%
SD	<1%	0%
TX	4%	3%
VA	1%	3%
VT	<1%	0%
WA	3%	<1%
WI	<1%	3%
WV	<1%	<1%
WY	1%	0%

Appendix Table 5

Distribution of Remaining Cases Compared with Initial Cases Selected for In-Depth Review By Agency/Individual Receiving Report

Agency/Individual	Remaining Cases Percent	Cases Selected for Review Percent
Food and Drug Administration	39%	54%
G. D. Searle and Company	32%	39%
Woodrow C. Monte	17%	6%
Arizona Health Department	11%	0%
James C. Turner	1%	1%
TOTAL	100%	100%

Appendix Table 6

Distribution of Remaining Cases by Date of Symptom Onset Compared with Initial Cases Selected for In-Depth Review

	Remaining Cases Percent	Cases Selected for Review Percent
1982		
June	1%	0%
July/August	2%	3%
September/October	2%	1%
November/December	1%	3%
1983		
January/February	6%	6%
March/April	5%	6%
May/June	10%	9%
July/August	15%	23%
September/October	16%	15%
November/December	16%	10%
1984		
January/February	18%	16%
March/April	3%	3%
Unable to identify month of onset*	4%	4%
TOTAL†	99%	99%

*Includes seven complaints in which the complainant was unsure of date of onset; estimated dates indicate time when aspartame was not generally available.

†Percent (%) may not total 100 due to rounding.

Appendix Table 7

Distribution of Remaining Cases
Compared with Initial Cases Selected for In-Depth* Review
By Major Categories†

Symptom Category	Remaining Cases Percent	Cases Selected for Review Percent
Neurological/Behavioral Only	54%	51%
Neurological/Behavioral + Gastrointestinal	14%	8%
Neurological/Behavioral + Allergic	5%	4%
Neurological/Behavioral + Menstrual	5%	3%
Gastrointestinal Only	11%	16%
Gastrointestinal + Allergic	1%	<1%
Allergic Only	7%	16%
Menstrual Only	2%	3%
Neurological/Behavioral + Gastrointestinal + Allergic	1%	0%
Neurological/Behavioral + Gastrointestinal + Menstrual	1%	0%
TOTAL§	101%	101%

*Excludes 32 cases reviewed for demographic data only.
†Excludes 15 cases with complaints in non-major categories only.
§Percent (%) may not total 100 due to rounding.

Appendix Table 8

Distribution of Remaining Cases*
By Neurological/Behavioral Symptoms

Symptoms	Percent	Number
Mood Alterations†	24%	104
Headache	20%	88
Dizziness	15%	63
Insomnia	7%	31
Fatigue	7%	30
Visual Impairment	6%	26
Memory Loss	4%	16
Seizures/Pre-seizures	3%	12
Numbness	2%	9
Fainting	2%	9
Disorientation	2%	9
Hallucinations/Pre-hallucinations	1%	6
Lack of Concentration	1%	6
Hyperactivity	1%	5
Motor Dysfunction	1%	5
Auditory Disturbances	1%	3
Ringing In Ears	<1%	2
Loss of Balance	<1%	1
Sleepwalking	<1%	1
Speech Impairment	<1%	1
Rush to Forehead	<1%	1
Paranoia	<1%	1
Nightmares	<1%	1
Behavioral Change	<1%	1
Personality Change	<1%	1
Loss of Sense of Taste	<1%	1
Drowsiness/Listlessness	0%	0
TOTAL NEUROLOGICAL/BEHAVIORAL SYMPTOMS		433

†*Mood Alterations:
- Agitation
- Anxiety
- Depression
- Hysteria
- Irritation
- Nervousness
- "Spaced-out"
- Suicidal
- Violent

*For comparison with neurological/behavioral cases selected for in-depth review, see Table 6-3, page 40.

Appendix Table 9

Distribution of Remaining Cases*
By Gastrointestinal Symptoms

Symptoms	Percent	Number
Nausea	35%	38
Diarrhea	22%	24
Abdominal Pain	19%	21
Other GI Symptoms†	13%	14
Vomiting	11%	12
TOTAL GI SYMPTOMS	100%	109

†Other GI Symptoms:

Symptom	Number
Bloated feeling	4
Gas	3
Activated preexisting colitis	1
Hiatal hernia	1
Pancreatitis	1
Burning in GI tract	1
Soreness in rectal area	1
Indigestion	1
Constipation	1
Total, Other GI	14

*For comparison with gastrointestinal cases selected for in-depth review, see Table 8-3, page 103.

Appendix Table 10

Distribution of Remaining Cases* By Allergic Symptoms

Symptoms	Remaining Cases Percent	Number
Sore Throat/Mouth	29%	13
Rash	24%	11
Itching	16%	7
Anaphylactic Reaction	2%	1
Other Allergic Symptoms†	29%	13
TOTAL ALLERGIC SYMPTOMS	100%	45

†Other Allergic Symptoms

Symptom	Number
Flushing	2
Swelling in toes	1
Choking and gasping for air	1
Constricted throat	1
Welts on bottom of feet	1
Welts on entire body	1
Shallow breathing	1
Pain in eyeballs	1
Sinus pain between nose and right eye	1
Facial swelling	1
Burning sensation in upper right arm	1
Burning in esophagus	1
Total, Other Allergic	13

*For comparison with allergic cases selected for in-depth review, see Table 7-3, page 84.

Appendix Table 11

Distribution of Remaining Cases
By Menstrual Symptoms

Symptoms	Remaining Cases Percent	Number
Irregular Menses	37%	11
Increased Menstrual Flow	13%	4
Decreased Menstrual Flow	13%	4
Menstrual Spotting	0%	0
Premature Menses	7%	2
Late Menses	7%	2
Other Menstrual Symptoms*	23%	7
TOTAL MENSTRUAL SYMPTOMS	100%	30

*Other Menstrual Symptoms

Symptom	Number
Painful menstrual periods	3
Spotting between periods	2
Vaginal bleeding	1
Continuous bleeding	1
Total, Menstrual	7

Appendix Table 12

Distribution of Remaining Cases By Miscellaneous Symptoms

Symptom	Number
Painful joints	11
Flu-like symptoms	8
Palpitations/racing heart	3
Chills/sweats	5
Sleepiness	4
Bladder dysfunction	3
Fever	3
Shortness of breath	3
Loss of hair	3
Coughing	3
Pressure in chest	2
Pressure in head	2
Increased appetite	2
Premature ventricular contractions	2
Pain in chest	2
Rise in blood glucose level	2
Loss of appetite	2
Strong odor in urine	2
Blood in urine	2
Urinary urge on awakening	1
Frequent urination	1
Extreme thirst	1
Swelling of ankles	1
Swelling in both hands	1
Rigid and stiff	1
Blackouts	1
Heart pain	1
Cramps on left side of body	1
Loss of strength	1
Numerous colds & infections	1
Back pain	1
Non-malignant tumor	1
Drop in blood pressure	1
Sensitivity to light	1
Hair growing on face (female)	1
Teeth crumbling	1
Unusual taste in mouth	1
Insulin shock	1
Charley horses	1
Cardiac arrest	1
Gray/black bar in left eye	1
Chipping of fingernails	1
Bitter taste	1
Earache	1
Lump in hip area	1
Rapid breathing	1
Left eye pain	1

CASE REPORT: CASES REVIEWED FOR DEMOGRAPHIC INFORMATION ONLY

V-0656: Acute Myocardial Failure, Group D

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.

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