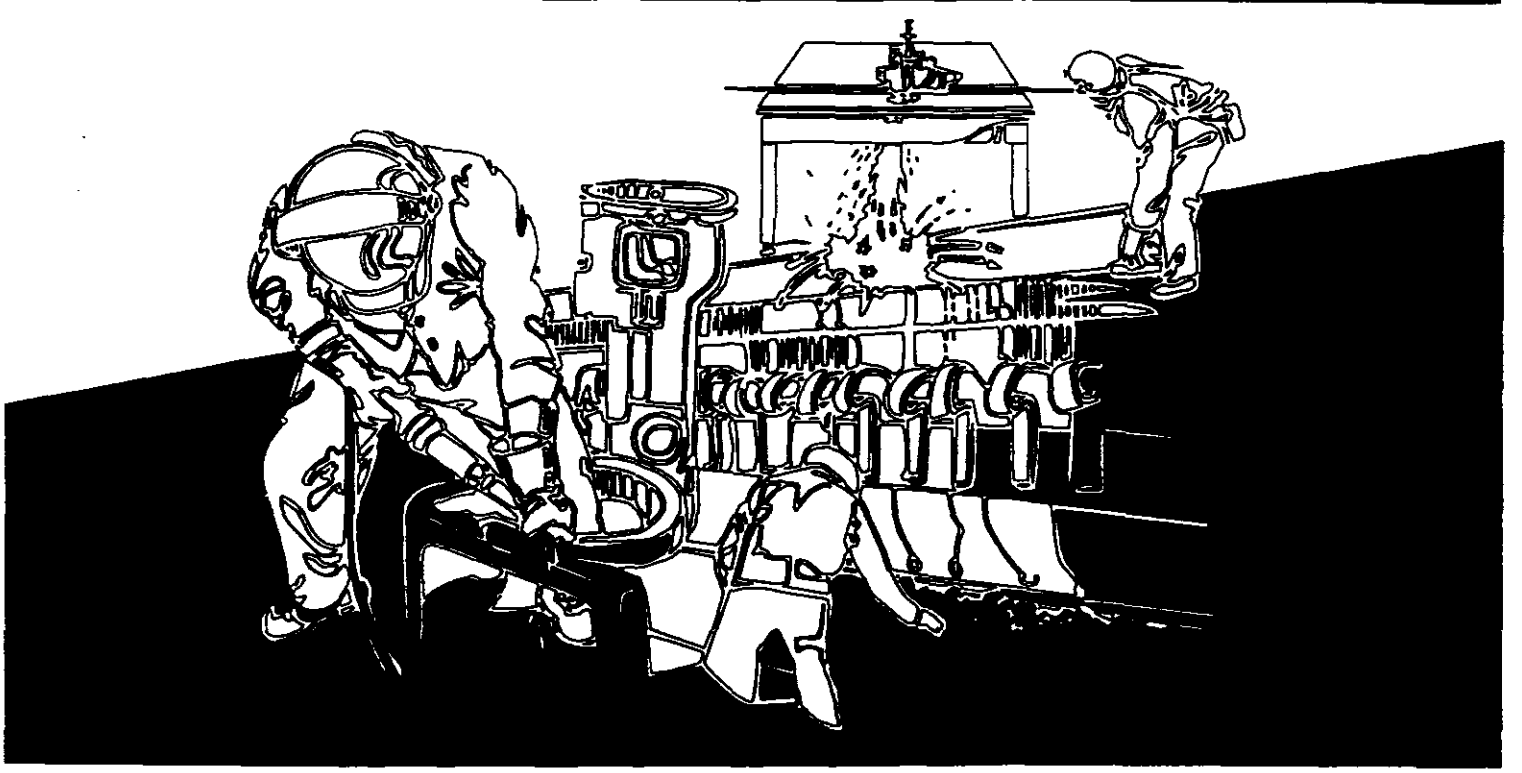
NIOSH

HEALTH HAZARD EVALUATION REPORT

HETA 86-035-2224
NABISCO BRANDS, INC.
SEVILLE, OHIO



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

CDC
CENTERS FOR DISEASE CONTROL

PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer and authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

The Hazard Evaluations and Technical Assistance Branch also provides, upon request, medical, nursing, and industrial hygiene technical and consultative assistance (TA) to federal, state, and local agencies; labor; industry; and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

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MAY 1992
NABISCO BRANDS, INC.
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NIOSH INVESTIGATORS:
GREGORY A. BURR, C.I.H.
BRUCE P. BERNARD, M.D., M.P.H.

SUMMARY

In October 1985, the National Institute for Occupational Safety and Health (NIOSH) received a request for a Health Hazard Evaluation (HHE) from the United Food and Commercial Workers Union Local 880 to investigate airway irritation symptoms among workers who were exposed to aspartame (*Nutrasweet®*) at the Seville, Ohio plant of Nabisco Brands, Inc. This facility processes and packages a variety of dry dessert and drink mixes. Aspartame, a food additive used in sugar-free food products, has been used at this Nabisco plant since approximately 1983.

A series of on-site surveys were conducted to evaluate work practices, assess employee exposures to airborne aspartame, and conduct a medical evaluation. Initial air sampling was conducted during 2 separate site visits (January and May 1987) to evaluate a new NIOSH sampling and analytical method for aspartame. In June 1990, as part of a more comprehensive evaluation at the facility, a total of 148 personal breathing zone and general area air samples for aspartame were collected over four consecutive days (June 4 to 7) over three shifts. The medical evaluation included a self-administered employee questionnaire, spirometry, peak expiratory flow volume rates (during waking hours), skin prick tests with specific workplace antigens, measurements of serum levels of Immunoglobulin E (IgE), and radioallergosorbent testing (RAST) for aspartame sensitization.

Results from the personal breathing-zone air samples for aspartame collected in June 1990 ranged from not detectable (ND) to 301 micrograms per cubic meter ($\mu g/m^3$). Area air samples collected during this same period ranged from ND to 83 $\mu g/m^3$. Both full-shift (up to 8-hours) and short-term air samples were collected throughout the facility at both sugar and sugar-free (i.e. using aspartame) weighing, blending, and packaging operations. There are no occupational exposure criteria specifically for aspartame.

The medical component of this HHE measured acute changes in the lung function, immunologic function and aspartame exposure status in workers reporting symptoms consistent with occupational asthma. Through a screening questionnaire, employees were invited to participate as "cases" if they reported two of three symptoms (chest tightness, shortness of breath, or wheezing) or wheezing alone since employment at Nabisco. "Controls" were selected at random from those reporting none of these symptoms. Clinical testing of the cases and controls by cross-work-shift spirometry, peak expiratory flow volume rates during waking hours (both in and out of the workplace), skin prick testing with specific workplace antigens, and measurements of serum levels of IgE and RAST for aspartame sensitization, failed to find any difference between the cases and controls. No relationship was found between airborne

aspartame exposure and respiratory symptoms or changes in peak expiratory flow rates (PEFR). There was also no relationship found between reported symptoms (including wheezing, shortness of breath, or chest tightness) recorded at the time of peak flow measurements and the presence of aspartame (measured by a personal air sample collected on every study participant on each day of the evaluation). There was no dose-response relationship for respiratory symptoms recorded during PEFR and exposure to aspartame.

No employee had a positive skin test to any of the following materials found in the plant:

Aspartame	Nutrasweet®
Fumaric Acid	Piperazine
Aspartame-HSA	Acetaldehyde
Sodium citrate	Disodium Phosphate

Two employees had positive skin tests to maleic acid-HSA (human serum albumin) and another employee had a positive reaction to tetrasodium pyrophosphate. Both chemicals are used at this facility.

Based on the information collected in this evaluation, NIOSH investigators did not find evidence for any occupationally-related lower respiratory disorder at this plant. There was no association between symptoms consistent with asthma and exposure to aspartame. These findings do not exclude the possibility that some employees may become allergic to aspartame. If this occurs, avoidance of further exposure may be necessary. During the course of this investigation recommendations were made to improve local exhaust ventilation in several areas of the manufacturing facility and to implement a respiratory protection program.

Keywords: SIC 2099 (Food Preparations, Not Elsewhere Classified), aspartame, pulmonary function tests, occupational asthma, work-related asthma, RAST testing.

INTRODUCTION

In October 1985, the National Institute for Occupational Safety and Health (NIOSH) received a request from the United Food and Commercial Workers Union Local 880 to investigate airway irritation symptoms among workers exposed to the artificial food sweetener aspartame (*Nutrasweet®*) at the Seville, Ohio plant of Nabisco Brands, Inc. This Nabisco plant blends and packages dry dessert and drink mixes. Aspartame has been used at this Nabisco plant in a variety of sugar-free products since late 1983.

Considering the unusually long period of time which transpired for completion of this Health Hazard Evaluation (HHE), a chronology of the more significant events which occurred during the conduct of this project is summarized in Appendix I.

BACKGROUND

An initial NIOSH site visit was conducted at the Nabisco plant on February 5, 1986. Of the approximately 275 employees working at the Seville plant at that time, about 30 were directly involved in the weighing, blending, or packaging of sugar-free products. Information obtained through confidential interviews with employees indicated that since late October 1985, the company had taken steps to reduce dust levels of several operations, including powder transfer at the weigh-out and blending stations. Several employees believed plant conditions were greatly improved since these control measures were enacted.

Following this initial visit, an environmental sampling and analytical method specifically for aspartame was developed by the Division of Physical Sciences and Engineering (DPSE) at NIOSH. During a follow-up survey on January 12-13, 1987, 26 full-shift air samples (both personal breathing-zone [PBZ] and general area [GA] air samples) were collected at weigh-out, blending, and packaging areas for aspartame. A third visit was conducted on May 5, 1987, where an additional 40 air samples were collected for aspartame. These included PBZ and GA air samples collected at sugar-free weigh-out stations, blending platforms and in various pudding and gelatin packaging areas. During a fourth follow-up visit on April 24, 1989, a medical questionnaire was distributed to all workers to identify employees with symptoms of occupational asthma.

The last NIOSH visit to the plant occurred on May 31 to June 7, 1990, at which time medical tests and air monitoring were performed. Using the medical questionnaire responses from the April 24, 1989 visit, NIOSH investigators identified all employees who reported having had any episode of wheezing and/or a combination of shortness of breath and chest tightness since their employment at Nabisco. These employees, and an equal number of asymptomatic workers, were invited to participate in a set of medical examinations. Because this return visit occurred more than one year following

the administration of the screening questionnaire (April 1989), a follow-up questionnaire was administered to the symptomatic and asymptomatic workers. A total of 75 employees met the criteria for participating in the study. Of these 75 workers, 40 employees did not wish to participate. The remaining 35 employees agreed to participate in the medical study; however, three of these 35 participants did not complete the medical examinations.

PROCESS DESCRIPTION

Originally constructed in 1962, this approximately 170,000 square foot manufacturing facility, employing about 275 workers at the time this evaluation was started, was purchased by Nabisco in 1981. The plant produces dry dessert and drink mixes in a wide variety of flavors. Production of sugar-free dessert mixes such as puddings and gelatins began at this facility in 1984. These sugar-free products contain aspartame (called APM by Nabisco management) in place of sugar or another sweetener. Other ingredients used in the plant include citric acid, gelatin, disodium phosphate, maltodextrin, and both natural and artificial colors and favors.

The process description, which is applicable for either sugar or sugar-free products, is described as follows:

1. WEIGH-OUT

   Following "recipes" suitable for each food product, employees manually weigh ingredients used in the dessert and drink mixes at "weigh-out" stations. The weighed ingredients are then individually packaged in plastic or paper bags. These weighed ingredients (termed a "batch") are collectively placed in a fiber drum for transportation to the adjacent blending department. Individual batches may weigh several hundred pounds depending on the type of dessert. Weigh-out operations are performed primarily on first shift.

2. BLENDING

   The individually packaged ingredients are mixed for approximately 20 to 30 minutes in large ribbon blenders and then gravity fed to a "tote" (a stainless steel container), which is used to transport the batch to the packaging line. Blending, like weigh-out, is primarily done on first shift.

3. PACKAGING

The totes are transported by lift trucks to the appropriate packaging line. One packaging machine operator, along with 2 to 4 helpers, dispense the bulk mix from the tote into individual boxes or envelopes. Packaging lines typically operate on both first and second shifts.

The sugar-free mixes constitute only a small fraction of total production at this plant. Typically, the sugar-free products are handled at specific weigh-out stations, blenders, and packaging lines to minimize the need for clean-up between product changes. Initial air monitoring for aspartame conducted in 1987 was limited to the weigh-out, blending, and packaging operations which only handled these sugar-free dessert mixes. The intent of this approach was to maximize the collection of any airborne aspartame that may have been present. In the subsequent comprehensive environmental and medical study conducted in 1990, air sampling for aspartame was conducted throughout the plant at both sugar and sugar-free operations.

EVALUATION CRITERIA

GENERAL

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH field staff employ environmental evaluation criteria for the assessment of a number of chemical and physical agents. These criteria are intended to suggest limits of exposure to which most workers may be exposed up to 10 hours per day, 40 hours per week for a working lifetime without experiencing adverse health effects. It is, however, important to note that not all workers will be protected from adverse health effects even though their exposures are maintained below these limits. A small percentage may experience adverse health effects because of individual susceptibility, a pre-existing medical condition, and/or a hypersensitivity (allergy). In addition, some hazardous substances may act in combination with other workplace exposures, the general environment, or with medications or personal habits of the worker to produce health effects even if the occupational exposures are controlled at the limit set by the criterion. These combined effects are often not considered in the evaluation criteria. Also, some substances are absorbed by direct contact with the skin and mucous membranes, and thus potentially increase the overall exposure. Finally, evaluation criteria may change over the years as new information on the toxic effects of an agent become available.

The primary sources of environmental evaluation criteria for the workplace are the following: 1) NIOSH Recommended Exposure Limits (RELs),[1] 2) the American Conference of Governmental Industrial Hygienists' (ACGIH) Threshold Limit Values (TLVs),[2] and 3) the U.S. Department of Labor, Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs).[3] The OSHA PELs may be required to take into account the feasibility of controlling exposures in various industries where the agents are used; the NIOSH RELs, by contrast, are based primarily on concerns relating to the prevention of occupational disease. In evaluating the exposure concentrations and the recommendations for reducing these concentrations found in this report, it should be noted that the lowest exposure criteria was used; however, industry is legally required to meet those limits specified by the OSHA standard.

A time-weighted average (TWA) exposure refers to the average airborne concentration of a substance during a normal 8- to 10-hour workday. Some substances have recommended short-term exposure limits (STELs) or ceiling values which are intended to supplement the TWA where there are recognized toxic effects from high short-term exposures.

SPECIFIC SUBSTANCES

Aspartame is the most widely used artificial food sweetener in the American food supply. About 200 times sweeter by weight than sugar, it was approved by the Food and Drug Administration (FDA) as a table-top sweetener and an ingredient in dry foods in 1981, for use in carbonated beverages in 1983, and subsequently in a number of other food products. Aspartame is a white, odorless, crystalline powder consisting of two amino acids, *l-aspartic acid and l-phenylalanine*. The Centers for Disease Control (CDC) investigated over 500 consumer complaints of various reactions attributed to sensitivity to the sweetener and found that 67 percent involved neurologic or behavioral symptoms, especially headaches.[4] Other case reports of adverse reactions to the sweetener among consumers have included migraine headaches, granulomatous panniculitis, and urticaria (hives).[5] The case reports of urticaria indicates that an allergic sensitization may occur in certain individuals consuming aspartame. This suggests that exposed workers may also be at risk for becoming sensitized, and exposure to airborne aspartame could cause adverse respiratory effects, including an allergic asthmatic response.

Previously, concerns about the ingestion of aspartame have centered on risks to phenylketonurics (individuals who do not properly metabolize phenylalanine), and the potential for aspartame to increase the level of excitatory neurotransmitters in the brain. As a result, a warning label appears on all products containing aspartame. The risk to phenylketonurics remains a point of controversy.[6,7]

There are no occupational exposure criteria for aspartame. The OSHA PELs for total and respirable particulates are based on the assumption that these materials are biologically inert and thus are not appropriate for aspartame.

EVALUATION DESIGN AND METHODS

Workers engaged in the manufacture or blending of aspartame are conceivably exposed, by inhalation, to doses many times greater than the general public if adequate engineering controls are not in place. This study compared acute changes in the lung function, immunologic status, and aspartame exposure in workers reporting symptoms consistent with occupational asthma to those not reporting symptoms.

SELECTION OF PARTICIPANTS

Participants were recruited from among all production workers who were working the day and swing shifts. A screening questionnaire was administered during the April 1989, site visit to every available employee on these shifts to identify workers with symptoms suggestive of occupational asthma. These were: 1) wheezing, 2) shortness of breath or difficulty breathing, and/or 3) chest tightness or pain, occurring since employment at Nabisco, and occurring less frequently or not at all on days away from work. In May 1990, all respondents from the April 1989 screening questionnaire who reported either: 1) wheezing, or 2) both shortness of breath or difficulty breathing **and** chest tightness or pain, occurring since employment at Nabisco were invited to participate in the follow-up case-control study. An equal number of respondents chosen at random from among those with none of these symptoms were also asked to participate in the case-control study.

Because of the time lapse between administration of the screening questionnaire and the actual study, all employees selected for participation from the April 1989 questionnaire, had follow-up interviews and screening questionnaires concerning symptoms of wheezing, shortness of breath, and chest pain which may have begun after April 1989. They were then re-classified as a case or control, or ineligible for the study, if they failed to meet the criteria listed above. If the participants' responses differed from their April 1989 responses, then their original screening questionnaire responses were discarded.

WORKPLACE AIR MONITORING

Sampling Methodology

A sampling and analytical method for measuring aspartame in air was developed by NIOSH chemists for this evaluation. This analytical method (NIOSH Method No. 5031) is provided in Appendix II. In brief, all of the personal breathing-zone

and general area air samples for aspartame were collected on 1.0 micron pore size, 37 millimeter diameter polytetrafluoroethylene (PTFE, also known as Teflon®) filters using a flow-rate of 2.0 liters per minute (a higher flow-rate was used on some short-term air samples). Laboratory experiments demonstrated excellent recovery of aspartame from the PTFE filters. It was also shown that aspartame does not migrate or decompose on the filter during sampling or when stored at ambient temperature for one month. Interferences from food additives, which were collected along with aspartame during actual field sampling, were absent.

Sampling Strategy

Personal breathing-zone and general area air samples were generally collected over the course of an entire work day. However, a limited number of short-term air samples were collected to evaluate "peak" exposures to aspartame which typically occurred during weigh-out or blending of sugar-free products.

All of the NIOSH on-site industrial hygiene evaluations, summarized in Table 1, were conducted to evaluate work practices and employee exposures to aspartame. The first series of personal and area air samples for aspartame was collected during a follow-up site visit to the Seville plant on January 12 and 13, 1987. Twenty-six full-shift air samples were collected for aspartame quantitation at weigh-out, blending, and packaging areas handling sugar-free products.

During the next follow-up survey on May 5, 1987, 40 air samples were collected for aspartame quantitation. These included PBZ and GA air samples collected at sugar-free (along with some sugar) weigh-out stations and blending platforms. Samples were also collected at various sugar and sugar-free pudding and gelatin packaging areas.

As part of the comprehensive medical and environmental follow-up study conducted between June 4-7, 1990, a total of 148 PBZ and GA air samples for aspartame were collected over all shifts. These data were used to determine exposure levels among the employees participating in the medical portion of the 1990 study and to correlate their aspartame exposures with their reported symptoms ant test results.

VENTILATION ASSESSMENT

Local exhaust ventilation (LEV) had been installed at each weigh-out station prior to the initial NIOSH site visit in February 1986. This system, consisting of one canopy hood situated directly over each weighing scale, was intended to collect any

particulate generated by the weighing-out process and thus reduce the employees' exposures to aspartame and other ingredients. Air flow measurements were made at the face of several canopy hoods during the January 1987, site visit.

Additional LEV systems were developed (or existing systems modified) at several blenders and packaging lines which handled sugar-free products. The intent of these systems was to lower employee exposures to aspartame and other particulates. These ventilation changes were made throughout the course of this NIOSH evaluation. No attempt was made to quantitatively evaluate the ventilation systems for the entire facility. Specific recommendations were made at several operations to either add additional ventilation or improve the existing LEV design. Many, if not all, of these changes have been made at this plant.

MEDICAL EVALUATION

To further evaluate the association of workplace exposure to aspartame and allergic sensitization and respiratory dysfunction, the following tests were performed on production workers with symptoms fulfilling the case definition of possible work-related asthma (cases) and workers without any respiratory symptoms (controls).

Questionnaire

All participants completed a self-administered questionnaire which addressed respiratory symptoms, and was based on previous questionnaires used by NIOSH in evaluating occupational asthma in the workplace.[8,9] Participants were asked to report the presence or absence of respiratory symptoms occurring in the last month, or wheezing since beginning work at Nabisco. Information was sought on whether symptoms followed certain activities or certain exposures at home and at work, and the time period in which symptoms would begin after exposure. Additional questions sought information on respiratory symptoms experienced on weekends away from the work site and on holidays. Participants also completed questions on smoking habits, occupational history, previous medical conditions, and the presence of other possible risk factors for asthma.

Peak Expiratory Flow Rates

To identify changes in the amount of air that could be exhaled over time (both in and out of the workplace), NIOSH investigators instructed participants on how to measure peak expiratory flow rate (PEFR), using a mini-Wright portable flow meter. Peak flow refers to the amount of air in liters per minute that can be blown through the flow meter in one sharp breath. Peak expiratory flow rates were measured, for a one week period, every three hours while the participant

was awake and during the night if she or he was awakened for any reason. Three exhalations were recorded each time, and the maximum of the three was recorded as the PEFR determination. Any wheezing, shortness of breath, chest tightness or cough experienced at the time of a PEFR determination was supposed to be reported on the peak flow record. A participant was considered to have significant bronchial lability if the difference between the minimum and the maximum PEFR on at least one day exceeded 20% of the day's maximum PEFR.[10]

Spirometry

To further identify obstructive airway changes that might be attributed to exposures in the sugar-free operation areas, NIOSH investigators measured pulmonary (lung) function. The purpose of the spirometry (breathing tests) was to determine if employees, as a group, had evidence of lung disease (particularly asthma). Spirometry was performed on two occasions for each participant: 1) immediately prior to work (approximately 0630 for day shift and 1600 hours for afternoon shift); and 2) within 30 minutes of the end of work (approximately 1400 hours for day shift and 2330 for afternoon shift). Spirometry was conducted by trained NIOSH spirometry technicians who were blind to exposure status.

Spirometry was performed according to ATS criteria[11] using two identical volume displacement spirometers (a SensorMedics model 822). The spirometers were calibrated with a 3-liter syringe before each pre- and post-work shift testing session. Each participant performed a minimum of five forced expiratory maneuvers in the standing position. For any given participant, pre- and post-shift spirometry was performed on the same spirometer. Values for forced vital capacity (FVC), forced expiration at one second ($FEV_{1,}$) and forced expiratory flow ($FEF_{25\%-75\%}$) were calculated by computer program (the AMPRO Z80 microprocessor) developed by NIOSH. These values were corrected to body temperature and pressure, saturated with water vapor (BTPS) and by the calibration factor determined before each pre- and post-work shift testing period.

Each spirometry value was compared to a predicted value calculated for age, sex, and height using the equations of Knudson.[12,13] (None of the participants were black, so race was not a consideration.) Test results were compared to the 95th percentile lower limit of normal (LLN) values calculated from Knudson's prediction equations to identify the abnormal lung disease patterns of obstruction and restriction. Spirometry values above the 5th percentile are considered normal while values falling below the 5th percentile are considered below the LLN.

Using this comparison, obstruction and restrictive patterns, for screening purposes, are defined as:

Obstruction: Observed rate of $FEV_1/FVC\%$ below the LLN.
Restriction: Observed FVC below the LLN.

The criteria for interpretation of the level of severity for obstruction and restriction, as assessed by spirometry, is based on NIOSH's classification scheme (available upon request). For those subjects with values below the LLN, the criteria are as follows:

	Obstruction ($FEV_1/FVC\%$)	Restriction (% Predicted FVC)
Mild	> 60 to < 70	>65
Moderate	> 45 to < 60	> 51 to < 65
Severe	< 45	<51

To examine cross-shift changes in spirometry, the percent change across the work shift was calculated for FEV_1 for each participant as follows:

Percent change (%) = 100 x (Postshift-Preshift)/Preshift

A criterion of 10% or greater decline in FEV_1 over a workshift was used as defining a clinically significant change. If a worker had an FEV_1 of less than three liters, a decrement of greater than 200 mL was used.[14]

The participants' personal sampling measurements for aspartame were noted on the days the individuals had cross-shift spirometry. If a participant was noted to have a greater than 10% decline in FEV_1, but no exposure to aspartame, the cross-shift change was not attributed to aspartame exposure.

Prior to both the pre-work shift and post-work shift spirometry, participants were interviewed about pulmonary symptoms, eating, recent upper respiratory infection, medications, and workplace exposure to both sugar and sugar-free product. If a participant had a recent upper respiratory infection, they did not take part in spirometry testing. Participants were instructed not to smoke for at least one hour prior to testing. If participants had smoked cigarettes or if they had eaten, they were asked to remain until one hour passed before having spirometry. Height was recorded and chest auscultation was performed by a physician. At post-shift testing, participants were also interviewed about the day's work activities and exposure to occupational and non-occupational

aspartame-containing foodstuffs. Chest auscultation was again performed by a physician.

Skin Prick Testing

Skin prick tests were used to determine if allergies had developed to chemicals currently used at Nabisco Brands, Inc. Skin prick testing was performed by two physicians trained in standard methods.[15] A drop of allergic solution, 1:20 (weight to volume) dilution, was aseptically placed on the cleansed forearm skin of the participants (cleansed with two isopropyl alcohol swabs). A sterile 26-gauge needle was inserted through the drop into the superficial skin and withdrawn with a slight lifting of the skin. A fresh disposable needle was used at each site. All tests were read at 10 and 20 minutes. A skin-test was considered positive if the wheal was as large as the positive controls or if a > 3 mm diameter wheal occurred. The skin panel included a commercial grade of aspartame, *NutraSweet®* (a blend of aspartame and dextrose), fumaric acid, diketopiperazine, aspartame-HSA (human serum albumin), maleic-HSA, acetaldehyde, sodium citrate, disodium phosphate, tetrasodium pyrophosphate, HSA, cherry flavor, strawberry flavor, orange flavor, yellow dye, orange Dye-Blend 56, and borate. This test panel also included common airborne allergens such as ragweed, Kentucky bluegrass, dust mite, and cat dander. Saline and histamine solutions were applied as negative and positive controls, respectively.

RAST and Immunoglobulin E (IgE) Testing

Two tubes of blood were drawn from each participant. One tube was tested by the radioallergosorbent method (RAST) for IgE specific to aspartame or its metabolite diketopiperazine. Results were expressed as counts per minute of ^{125}I-labeled anti-IgE bound to allergen-coated discs, and they were considered positive if the test sera binding was more than four standard deviations above the mean of non-exposed laboratory controls. One tube of blood was used to measure total IgE by the enzyme-linked immunoassay (ELISA) method. (IgE is an antibody produced by the body during allergic reactions.)

Statistical Analysis

Analyses were done using Statistical Analysis System (SAS) Version 6.03.[16] Differences in pulmonary function test results between cases and controls were evaluated using Student T-tests. Differences in questionnaire responses between cases and controls were evaluated by calculating odds ratios.

Exposure Status

Case Definition

The following epidemiologic case definitions for aspartame-related occupational asthma (AROA) were developed for this evaluation.

1. Respiratory symptoms temporally related to work, as reported on the most recent responses to the interview and screening questionnaire

AND

2. Symptomatic, significant bronchial lability temporally related to work. The criteria for significant bronchial lability was the participant's contemporaneous report of wheezing, shortness of breath, chest tightness or cough as his or her PEFR reached the minimum for the day. The bronchial lability was considered work-related if: a) the difference between the maximum and the minimum exceeded 20% on at least one work day; or b) if there was an obvious U-shaped appearance to the PEFR determination on a workday. (The U-shaped appearance suggests that the PEFR had fallen in response to work exposures and had risen towards the maximum upon the cessation of exposure.)

AND

3. At least one positive skin test or RAST to aspartame or the aspartame breakdown product 3-carboxymethyl-6-benzyl-2,5-diketopiperazine (diketopiperazine).

A participant was classified as having possible AROA if he/she fulfilled (1) and (2) above but had no positive skin test or RAST to aspartame or its breakdown product diketopiperazine. Alternately, a participant was classified as having possible AROA if he/she had respiratory symptoms believed to be related to work and at least one positive skin test or RAST to aspartame, but no evidence of significant symptomatic bronchial lability.

RESULTS

ENVIRONMENTAL

Results from the PBZ and GA air samples collected between 1987 and 1990 at the Seville, Ohio plant are presented in Tables 2, 3, and 4. As noted, both full-shift (up

to 8-hours) and short-term air samples were collected throughout the facility at both sugar and sugar-free (i.e. using aspartame) weigh-out, blending, and packaging operations. All of the air concentrations are expressed in micrograms of aspartame per cubic meter of air ($\mu g/m^3$).

Tables 5 and 6 compare the results of short-term (ranging up to 30 minutes in duration) and full-shift samples collected at sugar and sugar-free weigh-out, blending, and packaging operations. Table 7 contains the mean, range, and standard deviation [$SD_{(n-1)}$] calculated for all of the NIOSH air monitoring data collected between 1987 and 1990 at the Seville facility.

MEDICAL

Of the 75 employees eligible for participation in the investigation, 40 did not wish to participate. In addition, one employee who was currently being treated with antibiotics for bronchitis was excluded from the study. Demographic characteristics of the two groups are presented in Table 8. The groups were significantly different in height but not in sex, age, smoking status, or years employed at the plant.

Questionnaire

The self-administered questionnaire was completed by 17 employees meeting the case definition and 15 employees selected as controls. Symptom prevalences for the cases and controls are presented in Table 9. Because cases were selected if they had symptoms of chest-pain, wheezing, and shortness of breath, it is not unexpected that the symptom prevalences are consistently higher for cases compared to controls in the expanded respiratory questionnaire. Cases reported that respiratory symptoms tended to occur more frequently with activities and exposures in the workplace as opposed to home, and symptoms tended to begin immediately with exposure, both at home and at work. The controls stated that symptoms occurred both at home and in the workplace. The controls also reported that symptoms occurred immediately after exposure. Cases were more likely to have a family history of hay fever, eczema, or asthma (Table 10). Current cigarette smokers were more likely to experience symptoms than past-smokers and non-smokers, among both cases and controls (Tables 11 and 12).

Spirometry

Thirty-one participants had cross-shift spirometry. Cross-shift spirometry's were completed on 17 employees with respiratory symptoms meeting the case definition and 14 employees without symptoms. All but four had normal results

on all (both pre- and post-shift) individual spirometries. Of the four participants with abnormal spirometries, two were cases and two were controls. Three of these had "obstructive" spirometric patterns on both pre-shift and post-shift spirometric testing, which were essentially unchanged over the shift. All three of these employees with obstructive patterns were current cigarette smokers with greater than 15 pack years of smoking. Pulmonary examination by auscultation revealed that one participant had mild diffuse wheezing on pre-shift examination, but the wheezing was not heard on the post-shift pulmonary examination. Another participant showed a "restrictive" pattern on pre-shift spirometries, also unchanged on post-shift spirometric testing. Pulmonary examination by auscultation was normal in this participant.

Two of the 31 participants had significant cross-shift changes in their spirometries (greater than a 10% decrement over the shift). However, one individual was not exposed to aspartame on the day of his/her cross-shift spirometries, so this decrement was not attributable to aspartame exposure. The other participant who showed cross-shift spirometry changes was unable to master the technique of spirometry and thus had an insufficient number of acceptable, reproducible spirometric curves for valid analysis. This individual was excluded from the pooled analysis. (This was the only participant of the 31 participants who was unable to master the spirometry technique.)

Baseline, or pre-shiftwork spirometry results are presented in Table 13. The mean baseline FEV_1 percent predicted, FVC percent predicted, and FEV_1/FVC ratio values were not significantly different between the cases and the control group.

Table 14 presents the mean cross-shift change in FEV_1 and FVC, and the cross-shift percent change in FEV_1 for cases and controls. The mean change in FEV_1 in the cases was 0.09 liters compared with 0.04 liters in the controls, a difference which was not statistically significant ($p > .36$). The mean percent change in the cross-shift FEV_1 for the controls was 0.85% and for the cases was 3.49%.

Because not all the cases and controls were exposed to aspartame (by personal air sampling measurements) the day they completed the cross-shift spirometries, we analyzed separately those cases and controls who were exposed to aspartame the day of their spirometries. This analysis is presented in Table 15. There was no significant cross-shift change in FEV_1, FVC, or mean percent change in the cross-shift FEV_1.

Peak Expiratory Flow Rate (PEFR) Measurements

Thirty-one participants completed peak flow determinations on at least four days, the minimum we thought were needed to determine whether they had significant bronchial lability. There were no participants who had peak flow patterns which showed significant work-related bronchial lability. Four of the 31 participants had a single PEFR that was more than a 15% decrease from the day's maximum PEFR but that could not be clearly attributed to work and showed no pattern with exposure to aspartame.

Two participants, who reported a prior history of asthma and might be considered to have reactive airways, did report symptoms of shortness of breath and cough on three days of testing. However, they did not show any significant changes in PEFR concurrent with the symptoms, and there were no reports of symptoms with significant PEFR changes following the initial reported symptoms.

Skin-prick tests

Thirty-four participants had skin-prick testing. Two employees had positive reactions to maleic acid-HSA. One employee had a positive reaction to tetrasodium pyrophosphate. Seven employees reacted positively to dust mites, four to Kentucky blue-grass, two to ragweed, two to cat dander, and one borderline (weakly positive) reaction to HSA. No employee had a positive skin reaction to the following materials: aspartame, *Nutrasweet®*, fumaric acid, piperazine, aspartame-HSA, acetaldehyde, sodium citrate, or disodium phosphate.

Blood Tests

Thirty-four participants provided blood samples. None had a positive RAST for aspartame-or diketopiperazine-specific IgE, and none had an elevated serum concentration of total IgE.

Personal Air Sampling Results of Cases and Controls

Of the participants who received PBZ and GA air monitoring for aspartame, 9 (53%) cases and 13 (93%) controls had measurable levels of aspartame recorded on at least one day of testing. Mean levels of aspartame exposure were 17.8 $\mu g/m^3$ in the cases (range 1.11-234.2 $\mu g/m^3$), and 21.4 $\mu g/m^3$ in the controls (range 1.13-300.64 $\mu g/m^3$).

Cases of Aspartame-Related Occupational Asthma

No individual studied fulfilled the criteria for aspartame-related occupational asthma or possible AROA.

DISCUSSION

ENVIRONMENTAL

The results from the air sampling suggest that employees working with sugar-free product batches were episodically exposed to aspartame throughout the work day. As shown in Tables 5 and 6, the higher peak exposures occurred when the aspartame powder was manually handled during such activities as weigh-out or blending. No airborne aspartame was measured in PBZ or GA air samples collected at operations which handled only sugar batches. Air sampling performed over the years 1987 to 1990 suggest that both PBZ and GA air concentrations of aspartame at the Seville facility have decreased. This decrease could be due to a combination of factors, including the addition (or improvement) of LEV systems at the sugar-free weigh-out, blending, and packaging operations; daily fluctuations in the quantity of sugar-free product which is produced; and an overall decline in the amount of sugar-free products manufactured at the plant.

MEDICAL

To understand more fully our findings at the Nabisco plant, it is necessary to have a basic understanding of occupationally related asthma, how it is diagnosed, and what our results mean. Therefore, the discussion of the medical component of the study will be divided into three sections: 1) a discussion on occupational asthma; 2) a discussion of the findings of this NIOSH study; and 3) a discussion of recent aspartame studies and how they relate to our findings at the Nabisco plant.

Occupational Asthma

Asthma, a lung disorder characterized by reversible obstruction of the lung airway system (called the bronchial tubes) causes intermittent respiratory symptoms, including shortness of breath, wheezing, chest tightness, and cough. In occupational asthma, airway obstruction is caused or made worse by workplace exposure to dusts, fumes, gases, or vapors.[17] In the U.S., asthma occurs in about 5% of the general population; 2% of these cases are thought to be occupational.[18]

Four different mechanisms of occupational asthma have been defined:

1. *Direct airway irritation (reflex bronchoconstriction)*

   In this type of occupational asthma, the airways of the lung are irritated by many nonspecific agents such as cold air, dust particles, gases, and fumes. This type does not involve the body's immune system, and in most cases, the individual has a history of asthma prior to any occupational exposure. These people are considered to have abnormally reactive airways, and they generally develop symptoms of shortness of breath, chest tightness, cough, and wheezing immediately after exposure to occupational or other agents.

2. *Inflammatory bronchoconstriction*

   This type results from inhalation of irritant gases and vapors in very high concentrations. The irritant gases cause damage to the cells lining the bronchial airways and result in an "inflamed" airway. The individual has symptoms of shortness of breath, wheezing, chest tightness, and cough. Symptoms usually resolve within several weeks, but in some individuals the symptoms can persist following exposure (over extended periods) to low levels of many non-specific irritants.

3. *Pharmacologic bronchoconstriction*

   This type of occupational asthma happens when specific substances in the workplace cause an effect on the airways of the lung. Symptoms normally occur immediately after the exposure to the substance. Usually, this type involves a "dose-response relationship"; that is, the higher the amount of the specific substance to which one is exposed, the greater the response of the lung (more obstruction of the airway, more mucous production, and more asthma). For example, certain pesticides (organophosphates) interfere with the action of an enzyme in the body, cholinesterase, and one result of this interference is obstruction of the airways, which brings on asthma symptoms. The more exposure to the organophosphate pesticide, the worse the asthma symptoms.

4. *Allergic bronchoconstriction or Type I hypersensitivity*

   This is the most common type of occupational asthma. Workers develop antibodies after being exposed to substances at work, and repeated exposure causes asthma to develop. The time between developing asthma symptoms after exposure to the workplace substance can vary from weeks to years. Once asthma has developed, symptoms may

occur immediately after exposure, following a delay of several hours, or in a pattern with both early and late components. Over 200 agents in U.S. workplaces have been found to cause occupational asthma. This is the type of asthma that we were investigating at Nabisco.

Case-Control Study

The series of medical tests failed to find any cases of occupational asthma or any significant differences in respiratory function between the cases and controls. Even among the potential cases, selected because of reported symptoms suggestive of asthma, the medical testing did not yield any evidence of occupational asthma. But since the participation rate was low, cases of occupational asthma may have gone undetected.

We found no relationship between aspartame exposure (by PBZ or GA air sampling measurements) and respiratory symptoms or changes in peak expiratory flow rates. There was also no relationship found with reported symptoms (including wheezing, shortness of breath, chest tightness) recorded prior to the peak flow measurements and the amount of aspartame measured by personal air sampler for each day measured. We did find that controls were more likely to be exposed to aspartame than cases (92% compared to 53%), the reverse of what would be expected if AROA was present. Cases were more likely to have a history of hay fever, eczema, and asthma, and were more likely to be current smokers.

Other Studies of Aspartame

Previous reports of adverse effects from aspartame exposure focused on **ingestion** of aspartame, as opposed to **inhalation** of aspartame, which was the focus of our study. Those reports, concerned with a possible immunologic or allergic response, include 65 of the approximately 500 CDC consumer complaints consistent with allergy, including gastrointestinal distress, urticaria, rhinitis, and wheezing.[4] Two case reports of aspartame-induced urticaria have been documented in a double-blind oral challenge study.[19]

Leon, et al. (1989) evaluated the effects of long-term oral administration of 75 mg/kg of aspartame per day with the use of a double-blind, placebo-controlled study in 108 volunteers.[20] Subjects received either aspartame or placebo (cellulose pills) in capsule form three times a day for 24 weeks. Results pertinent to the Nabisco study include the finding that both groups, the one receiving aspartame **and** the one receiving placebo, commonly reported upper respiratory tract symptoms. The authors concluded that these reported symptoms were not due to aspartame because those exposed to aspartame

reported about the same percentage of respiratory symptoms as those not exposed to aspartame. Overall, there were no statistical differences between the groups in the number of subjects experiencing symptoms or in the number of symptoms per subject.

Garriga, et al. (1991) initiated a study to identify subjects with hypersensitivity reactions to aspartame with blinded challenge procedures.[21] Sixty-one self-referrals and physician referrals were screened, with 20 referrals evaluated in the clinic. Sixteen of the 20 subjects underwent skin prick testing for aeroallergens, selected foods, aspartame and diketopiperazine, and had plasma histamine levels drawn. Twelve subjects had single- and double-blinded oral challenge testing with up to 2000 mg of aspartame, with pre- and post-challenge FEV_1 spirometry readings. Results showed that three of the 16 subjects had a positive skin test to aspartame, although in each case the reaction was only 4 to 5 mm greater than the reaction at the control site (a positive test was greater than 3 mm larger than the wheal diameter at the negative control site). Two of these subjects with positive skin tests had oral challenge tests which were negative (the other subject did not have challenge testing). The authors stated that in the absence of a clear and reproducible immediate reaction to aspartame, it was impossible to evaluate the accuracy of skin testing with aspartame in predicting clinical aspartame sensitivity. No subject was found to have a positive oral challenge test, and plasma histamines remained unchanged. They concluded that it is difficult to find and study aspartame-sensitive subjects and they failed to find anyone with a clearly reproducible adverse reaction to aspartame. This finding was consistent with the biology of aspartame, they concluded. Aspartame is a dipeptide, does not appear to react specifically with any antibody or cell (e.g. as a hapten), and is rapidly degraded intracellularly at the brush border of cells into its two amino acids.

Szucs, et al. (1986) found that special allergic response cells, called mast cells, are **not** stimulated or degranulated by aspartame.[22] Mast cell granules are released by the body when stimulated by IgE, which "senses" the presence of an allergen. These granules help precipitate allergic symptoms. Aspartame was not found to stimulate mast cell degranulation in vitro (in the laboratory) or in vivo (in animals or human subjects). These findings support our study results that aspartame did not cause an allergic asthma in any of the individuals tested (both those who had reported symptoms and those who did not).

Limitations of the Study

The study design used in this evaluation of Nabisco food production workers has a number of strengths and weaknesses in assessing the respiratory symptoms experienced by the employees. It is a study of a relatively small

population in a single building. The study design afforded the opportunity to observe workers' health experience during the same week that measurements of aspartame was completed. There was a relatively high participation rate in the screening phase of the study (around 85%) used to identify potential cases and controls, minimizing the potential for selection bias. However, there was a relatively low participation rate (45%) among the cases and controls selected for the medical tests, possibly introducing selection bias. This type of bias means that workers who agree to participate might not be representative of all those eligible. For example, persons with more health problems might tend to volunteer for participation in the study, whereas people with minor problems or no problems may not. Or perhaps, persons whose health problems have already been diagnosed, or under treatment, may not feel the need to participate. Thus, the findings of a study with a low participation rate may over- or under-estimate the effects of the exposure of concern.

Over the four year period in which this hazard evaluation took place there have been additions and improvements in local exhaust ventilation throughout the plant and changes in the processing of aspartame-containing products. It is the opinion of NIOSH investigators that these changes have decreased the workers' PBZ exposures to aspartame. However, because we found no dose-response relationship between aspartame and health effects (indeed, the controls had greater exposure), this decreasing exposure probably did not affect the study's outcome.

VENTILATION ASSESSMENT

Weigh-out Department

Ventilation measurements were made at weigh-out stations nos. 1 through 5 during the January 1987 NIOSH survey. These measurements were made at the canopy hoods which were installed in 1986.* Fifty-five gallon drums, used by the workers to hold the batch ingredients once they are weighed, were positioned one to two feet in from of the hood. Hand scoops are used to transfer ingredients. Average face velocities at the canopy hoods ranged from 78 to 112 feet per minute (fpm). An average airflow of approximately 50 fpm

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*When originally installed in January 1986 the canopy hoods were located directly above the scales used to weigh the ingredients, a position which would draw any generated particulates *up and through* the workers' breathing zone. The NIOSH investigators recommended that these hoods be turned and positioned behind the weigh-out station to *exhaust* the particulates away from the employee.

when measured six inches from the face of the canopy hood decreased to near zero when measured directly over the fiber drums from which the employees removed the bulk ingredients.

Blending

Some blenders, including the one used to blend the sugar-free gelatins, were equipped with LEV to help control the dust generated during the blending process. The designs were similar and consisted of a hood positioned near the blender opening which was intended to capture any dust released while the ingredients were manually added to the blender. Although no airflow measurements were made at these hoods, visual observation indicated that the design functioned as intended. We recommended, however, eliminating the excess flexible duct connecting the exhaust hoods to the fixed ventilation system.

Dessert Packaging Lines

The company had installed LEV systems on several packaging lines to control the dust released during packaging. One design consisted of exhaust ducts positioned near the "point-of-fill" to capture any residual dust. Another more elaborate ventilation design involved a locally exhausted clear plastic enclosure which surrounded the product dispensing and package filling operations. We made no ventilation measurements to evaluate either design, but both appeared (by visual observation) to operate effectively.

CONCLUSIONS

We did not find evidence of occupationally-related asthma at the Nabisco plant. There was no association between symptoms consistent with asthma and exposure to aspartame.

This study does not completely eliminate the possibility that some individuals may become allergic to aspartame. If a worker becomes sensitized, avoidance from further exposure may be necessary. Further evidence of aspartame sensitivity can be examined through the application of blinded challenge procedures at medical institutions having those capabilities.

RECOMMENDATIONS

1. The design of the local exhaust ventilation system at each weigh-out station can be modified to improve the capture efficiency of the exhaust hood. Excessive (and unnecessary) lengths of flexible duct connecting the exhaust

hood to the fixed metal duct increases air resistance and decreases capture effectiveness. Enclosing one or more sides of the exhaust hood (at the time of this evaluation all four sides were open) should also improve the capture ability of the exhaust hood.

The following recommendations, which extend beyond the original scope of this survey, are based on observations by NIOSH investigators during the course of this evaluation. These recommendations involve noise, respiratory protection, emergency eye wash stations, and other personal protective equipment such as gloves and safety shoes. Many of these recommendations have already been implemented at the Seville facility.

2. At the recommendation of NIOSH investigators, the written respiratory protection program for the Seville facility was expanded to include all of the basic elements required in the OSHA General Industry Standards, 29 Code of Federal Regulations (CFR) Part 1910.134.

3. At the recommendation of NIOSH investigators, an emergency eye wash station was installed near the weigh-out and blending areas of the plant and several emergency eye wash bottles were removed from the work area.

4. To improve personal hygiene, waterless hand cleaners and disposable towels (or a wash basin) should be installed in the weigh-out area since some of the materials handled by the employees can cause skin irritation on contact. (There were no toilet facilities in or near the weigh-out department.)

5. At the beginning of this evaluation the cotton gloves used by workers were available in only one size (medium). Other sizes (such as small and large) should be made available to the workers.

6. At the recommendation of NIOSH investigators, the height of an entrance to the instant pudding packaging area was raised by removing one row of cinder blocks.

7. Employees working in the weigh-out department should wear safety shoes. Workers routinely move 55 gallon drums of ingredients which may weigh as much as 250 pounds.

8. Noise levels in several areas of the plant (such as on Line 15) could be reduced by the installation of silencers on compressed air nozzles.

9. Although recognized as a high noise area by Nabisco management, no hearing protection signs were posted at the two entrances to the room

housing blender #7. The noise levels generated by the vibrating screen on blender #7 may be reduced by the use of dampening materials to avoid metal-to-metal contact.

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AUTHORSHIP AND ACKNOWLEDGEMENTS

Report Prepared by:	Gregory A. Burr, C.I.H. Supervisory Industrial Hygienist Industrial Hygiene Section Bruce Bernard, M.D., M.P.H. Supervisory Medical Officer Hazard Evaluations and Technical Assistance Branch Division of Surveillance, Hazard Evaluations, and Field Studies
Field Assistance by:	William Albrecht, M.D., C.I.H. Richard L. Stephenson, C.I.H. Robert F. Mouradian, Ph.D. Gregory M. Kinnes, M.S. Michael E. Barsan Boris Lushniak, M.D., M.P.H. Marian Colemen Jim Collins
Laboratory Services:	David I. Bernstein, M.D. Division of Immunology, University of Cincinnati College of Medicine
Analytical Method Developed by:	Charles E. Neumeister Division of Physical Science And Engineering
Other NIOSH Investigators:	Jou-Fang Deng, M.D. Thomas Hales, M.D. Thomas Sinks, M.D.
Originating Office:	Hazard Evaluations and Technical Assistance Branch Division of Surveillance, Hazard Evaluations, and Field Studies

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1. United Food and Commercial Workers Union Local 880
2. Nabisco Brands, Inc., Seville, Ohio
3. Corporate Office, Nabisco Brands, Inc., Seville, Ohio
4. OSHA Region V

For the purpose of informing affected employees, copies of this report shall be posted by the employer in a prominent place accessible to the employees for a period of 30 calendar days.

TABLE 1
Surveys Conducted at Nabisco Brands, Inc.
Seville, Ohio
HETA 86-035

SITE EVALUATION	DATE	ACTIVITIES
Initial	2/5/86	Opening conference, walk-through of the facility, collection of bulk samples.
Follow-up No. 1	1/13-14/87	Twenty-six personal and general area air samples for aspartame collected in weigh-out, blending and packaging areas (sugar-free operations only). No medical component.
Follow-up No. 2	5/5/87	Forty personal and general area air samples for aspartame collected in weigh-out, blending and packaging areas (both sugar and sugar-free operations). No medical component.
Follow-up No. 3	4/24/89	Medical questionnaire distributed to all plant employees to identify workers with symptoms of occupational asthma. No industrial hygiene component.
Follow-up No. 4	5/31 to 6/7/90	Personal air monitoring for aspartame conducted on all study participants over 4 consecutive workdays. General area air sampling conducted throughout the facility over the course of this follow-up visit. Each participant in the medical portion of the HHE received a questionnaire, pulmonary function test, blood tests (for specific immunoglobulins), peak expiratory flow measurements, and skin prick tests for aspartame and other substances.

TABLE 2
PERSONAL AND GENERAL AREA AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
JANUARY 13-14, 1987

Location	Date	Sample Number	Sample Type	Start (HH:MM)	Stop (HH:MM)	Volume liters	Concentration (ug/M3)
Operator, Pudding Line	1/13/87	GB-1	Personal	07:13	15:52	1163	7
Packer, Gelatin Line	1/13/87	GB-2	Personal	06:54	15:50	1183	30
Packer, Gelatin Line	1/13/87	GB-3	Personal	07:03	15:51	1183	10
Operator, Blending and Weigh-out	1/13/87	GB-5	Personal	06:46	14:51	1213	102
Packer, Pudding Line	1/13/87	GB-6	Personal	07:11	15:54	1168	(2)
Operator	1/13/87	GB-7	Personal	06:56	15:52	1183	100
Blender	1/13/87	GB-8	Personal	06:40	14:45	1218	40
Packer, Pudding Line	1/13/87	GB-9	Personal	07:08	14:24	1133	(2)
Weigh-out, SF products	1/13/87	GB-10	Personal	06:45	14:47	1215	132
Area Sample, Blender No. 7	1/13/87	GB-11	Area	07:39	15:08	4939	15
Area Sample, Blender No. 8	1/13/87	GB-12	Area	07:27	15:14	4250	(3)
Area Sample, Weigh-out Station	1/13/87	GB-13	Area	07:47	15:11	3863	12
Operator, Gelatin Line	1/14/87	GB-14	Personal	06:35	14:36	1180	70
Packer, Gelatin Line	1/14/87	GB-15	Personal	06:39	14:44	1218	7
Packer, Gelatin Line	1/14/87	GB-16	Personal	06:41	14:46	933	(3)
Packer, Pudding Line	1/14/87	GB-17	Personal	06:45	14:50	1218	ND
Packer, Pudding Line	1/14/87	GB-18	Personal	06:46	14:48	1075	(4)
Operator, Weigh-out	1/14/87	GB-19	Personal	06:49	14:45	1093	55
Operator, Weigh-out	1/14/87	GB-20	Personal	06:50	13:05	630	13
Operator, Weigh-out	1/14/87	GB-21	Personal	06:51	14:46	1098	26
Operator, Weigh-out	1/14/87	GB-22	Personal	13:23	14:52	220	545

TABLE 2
PERSONAL AND GENERAL AREA AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
JANUARY 13-14, 1987

Location	Date	Sample Number	Sample Type	Start (HH:MM)	Stop (HH:MM)	Volume liters	Concentration (ug/M3)
Area Sample, Blender No. 8	1/14/87	GB-23	Area	07:31	16:07	4489	35
Area Sample, Weigh-out Station	1/14/87	GB-26	Area	07:00	16:09	4996	24
Area Sample, Blender No. 7	1/14/87	GB-27	Area	07:04	16:15	6061	(5)

COMMENTS:

1. There are no specific OSHA, NIOSH, or ACGIH exposure limits for aspartame.
2. Concentrations shown in brackets are between the limit of detection and limit of quantitation for that sample.
3. ND = None detected.
4. All personal and general area air samples were collected at operations which were weighing, blending, or packaging sugar-free products.

TABLE 3
PERSONAL AND GENERAL AREA AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
MAY 5, 1987

Location	Date	Sample Number	Sample Type	Start (HH:MM)	Stop (HH:MM)	Volume liters	Concentration (ug/M3)
Operator, Pudding Line	5/5/87	GB-1	Personal	06:39	06:54	38	ND
Operator, Blender No. 7	5/5/87	GB-2	Personal	06:45	07:07	55	ND
Operator, Weigh-out Station	5/5/87	GB-3	Personal	06:45	07:15	75	ND
Area Sample, Pudding Lines 1 and 2	5/5/87	GB-4	Area	06:59	14:42	1160	ND
Operator, Pudding Line	5/5/87	GB-5	Personal	06:54	07:29	88	ND
Operator, Blender No. 7	5/5/87	GB-6	Personal	07:07	07:37	75	ND
Operator, Weigh-out Station	5/5/87	GB-7	Personal	07:15	07:48	83	ND
Area Sample, Weigh-out station	5/5/87	GB-8	Area	07:13	15:04	1180	5.1
Area Sample, Weigh-out Room	5/5/87	GB-9	Area	08:20	15:03	1010	(2.0)
Area Sample, Gelatin Lines 3 and 4	5/5/87	GB-10	Area	07:44	14:49	1068	ND
Area Sample, Lines 10 and 11	5/5/87	GB-11	Area	07:39	14:52	1093	ND
Operator, Blender No. 7	5/5/87	GB-12	Personal	07:37	08:14	93	140
Operator, Weigh-out Station	5/5/87	GB-13	Personal	07:57	08:27	75	133
Operator, Blender No. 7	5/5/87	GB-14	Personal	08:14	08:44	75	ND
Operator, Pudding Line	5/5/87	GB-15	Personal	07:29	08:00	78	ND
Operator, Pudding Line	5/5/87	GB-16	Personal	08:00	08:36	90	ND
Operator, Weigh-out Station	5/5/87	GB-17	Personal	10:03	10:33	75	147
Operator, Blender No. 7	5/5/87	GB-18	Personal	09:59	10:29	75	213
Operator, Blender No. 7	5/5/87	GB-19	Personal	10:29	11:10	103	ND
Operator, Weigh-out Station	5/5/87	GB-20	Personal	10:33	11:04	78	ND
Operator, Weigh-out Station	5/5/87	GB-21	Personal	11:04	11:34	75	ND
Operator, Blender No. 7	5/5/87	GB-22	Personal	11:10	12:46	118	153

TABLE 3
PERSONAL AND GENERAL AREA AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
MAY 5, 1987

Location	Date	Sample Number	Sample Type	Start (HH:MM)	Stop (HH:MM)	Volume liters	Concentration (ug/M3)
Operator, Blender No. 7	5/5/87	GB-23	Personal	12:46	13:16	78	ND
Operator, Weigh-out Station	5/5/87	GB-24	Personal	12:11	12:49	95	432
Operator, Weigh-out Station	5/5/87	GB-25	Personal	12:49	13:19	75	ND
Operator, Blender No. 7	5/5/87	GB-26	Personal	13:17	13:52	88	ND
Operator, Weigh-out Station	5/5/87	GB-27	Personal	13:19	13:53	85	ND
Operator, Blender No. 7	5/5/87	GB-28	Personal	13:52	15:01	173	197
Operator, Weigh-out Station	5/5/87	GB-29	Personal	13:53	14:38	113	ND
Area Sample, Weigh-out Station	5/5/87	GB-30	Area	15:28	22:25	1045	ND
Area Sample, On lift truck	5/5/87	GB-31	Area	15:21	22:15	1040	(3.8)
Area Sample, Weigh-out Station	5/5/87	GB-32	Area	16:22	22:28	915	ND
Area Sample, Blender No. 5	5/5/87	GB-33	Area	16:19	22:21	910	ND
Area Sample, Gelatin Packaging	5/5/87	GB-35	Area	15:19	22:09	1030	ND
Area Sample, Weigh-out Room	5/5/87	GB-36	Area	15:27	22:23	1045	ND
Area Sample, Pudding Packaging	5/5/87	GB-37	Area	15:17	22:08	1030	ND
Area Sample, Cheesecake Packaging	5/5/87	GB-38	Area	15:23	22:11	1028	ND

COMMENTS:

1. There are no specific OSHA, NIOSH, or ACGIH exposure limits for aspartame.
2. Concentrations shown in brackets are between the limit of detection and limit of quantitation for that sample.
3. ND = None detected.

TABLE 4
PERSONAL AND GENERAL AREA AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
JUNE 4-7, 1990

Location	Date	Sample Number	Sample Type	Start (HH:MM)	Stop (HH:MM)	Volume liters	Concentration (ug/M3)
Blender (area not specified)	6/4/90	102	Personal	07:31	14:23	736	ND
Fork Truck Operator	6/4/90	103	Personal	07:42	14:38	833	4.8
Mechanic, Line 5	6/4/90	104	Personal	07:15	14:21	853	ND
Technician, QC Lab	6/4/90	105	Personal	07:25	14:25	841	ND
Packer, Lines 24 & 25 (SF* Gelatin)	6/4/90	106	Personal	06:58	14:32	909	8.8
Operator, Line 4 (S** Gelatin)	6/4/90	107	Personal	06:40	14:30	941	ND
Packer, Line 10 (SF Pudding)	6/4/90	108	Personal	07:08	14:18	861	2.3
Packer, Lines 24 & 25 (SF Gelatin)	6/4/90	109	Personal	06:31	14:36	971	9.4
Fork Truck Operator	6/4/90	110	Personal	06:15	14:45	950	ND
Packer, Line 3	6/4/90	111	Personal	06:48	14:19	903	ND
Operator, Lines 24 & 25 (SF Gelatin)	6/4/90	112	Personal	06:40	14:48	918	4.4
Operator, Blender #1	6/4/90	116	Personal	06:55	14:27	886	5.6
Maintenance Worker	6/4/90	117	Personal	06:51	14:49	957	3.1
Operator, Weigh-out Station	6/4/90	118	Personal	07:05	14:31	893	6.7
Operator, Blenders #2 & 8	6/4/90	119	Personal	06:59	14:25	893	37
Technician, QC Lab	6/4/90	120	Personal	07:23	14:50	895	1.1
Packer, Line 90	6/4/90	121	Personal	07:20	14:42	885	4.5
QC Manager	6/4/90	122	Personal	07:15	14:35	800	2.5
Operator, Weigh-out Station	6/4/90	123	Personal	07:07	14:30	887	16
Operator, Line 1	6/4/90	125	Personal	15:30	23:03	907	ND
Maintenance (Plant Wide)	6/4/90	126	Personal	19:42	02:03	668	1.5
Line 5 General Area (S)	6/4/90	127	Area	15:51	23:20	899	ND
Line 10 General Area (SF)	6/4/90	128	Area	15:57	23:07	861	ND

TABLE 4
PERSONAL AND GENERAL AREA AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
JUNE 4-7, 1990

Location	Date	Sample Number	Sample Type	Start (HH:MM)	Stop (HH:MM)	Volume liters	Concentration (ug/M3)
Packer, Lines 24 & 25 (SF Gelatin)	6/4/90	129	Personal	15:20	23:11	943	16
Packer, Line 10 (SF Pudding)	6/4/90	130	Personal	15:07	01:10	1124	3.6
Packer, Lines 24 & 25 (SF Gelatin)	6/4/90	131	Personal	15:15	01:11	1196	15
Operator, Line 11 (SF Pudding)	6/4/90	132	Personal	15:05	01:17	1212	1.7
Packer, Line 10 (SF Pudding)	6/4/90	134	Personal	15:09	23:06	955	ND
Technician, QC Lab	6/4/90	135	Personal	15:38	23:14	913	2.2
Packer, Lines 24 & 25 (SF Gelatin)	6/4/90	136	Personal	15:23	01:14	1190	71
Blender (Group Leader)	6/4/90	138	Personal	15:47	23:18	820	3.7
Technician, QC Lab	6/4/90	139	Personal	15:41	23:02	883	10
Line 10, Machine 5 area	6/5/90	200	Area	16:52	23:29	795	ND
Packer, Lines 24 & 25 (SF Gelatin)	6/5/90	201	Personal	06:15	14:27	985	46
Packer, Lines 9 & 10 (SF and S)	6/5/90	202	Personal	06:15	14:35	1001	6.0
Packer, Lines 24 & 25 (SF Gelatin)	6/5/90	203	Personal	06:15	14:28	987	9.1
Operator, Lines 3 & 4	6/5/90	204	Personal	06:20	14:41	1003	ND
Packer, Line 11 (SF Pudding)	6/5/90	205	Personal	06:20	14:38	997	ND
Operator, Lines 24 & 25 (SF Gelatin)	6/5/90	206	Personal	06:25	14:29	969	6.2
Technician, QC Lab	6/5/90	207	Personal	06:25	14:50	1011	3.0
Operator, Line 3	6/5/90	208	Personal	06:30	14:41	983	ND
Fork Truck Operator	6/5/90	209	Personal	06:30	14:32	900	ND
Maintenance (Plant Wide)	6/5/90	210	Personal	06:40	12:16	672	4.5
Fork Truck Operator	6/5/90	211	Personal	06:50	14:30	921	4.4
Mechanic (Plant Wide)	6/5/90	212	Personal	07:00	14:25	891	ND
Packer, Line 11 (SF Pudding)	6/5/90	214	Personal	16:02	23:06	849	1.2

TABLE 4
PERSONAL AND GENERAL AREA AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
JUNE 4-7, 1990

Location	Date	Sample Number	Sample Type	Start (HH:MM)	Stop (HH:MM)	Volume liters	Concentration (ug/M3)
Technician, QC Lab	6/5/90	215	Personal	17:59	23:00	602	22
Packer, Lines 24 & 25 (SF Gelatin)	6/5/90	217	Personal	15:40	23:08	897	234
Technician, QC Lab	6/5/90	218	Personal	15:46	23:08	885	1.1
Fork Truck Operator	6/5/90	219	Personal	15:44	23:11	895	44
Operator, Line 1 (S Pudding)	6/5/90	220	Personal	15:40	23:00	881	ND
Operator, Blender # 3	6/5/90	221	Personal	06:36	14:36	961	1.0
Operator, Weigh-out Station	6/5/90	222	Personal	06:38	14:42	902	26
Operator, Weigh-out Station	6/5/90	223	Personal	06:40	14:49	979	7.2
Operator, Weigh-out Station	6/5/90	224	Personal	06:42	14:44	965	301
Manager, QC Lab	6/5/90	225	Personal	06:45	14:54	716	ND
Operator, Blender # 5	6/5/90	226	Personal	06:51	14:43	876	2.3
Operator (float), Lines 1,2,3,4	6/5/90	227	Personal	07:05	14:46	923	ND
Operator, Blender # 2	6/5/90	228	Personal	07:28	14:58	901	4.4
Line 3, Machine 5 Area	6/5/90	229	Area	08:29	15:07	797	ND
Weigh-out area, near Station #1	6/5/90	230	Area	08:37	15:09	785	83
Weigh-out area, near Station #5	6/5/90	231	Area	08:41	15:10	778	17
Line 10, Machine 15 Area	6/5/90	232	Area	08:48	15:14	772	ND
Line 24 Area (SF Gelatin)	6/5/90	233	Area	08:56	15:17	762	24
Packer, Line 2	6/5/90	234	Personal	16:05	23:05	841	2.4
Fork Truck Operator	6/5/90	235	Personal	16:16	23:22	853	2.4
Packer (relief), Lines 1,2,3,4	6/5/90	236	Personal	16:20	23:14	829	ND
Line 3 Area	6/5/90	237	Area	16:45	23:25	801	ND
Room used for skin test	6/5/90	238	Area	16:59	23:35	793	ND
Weigh-out area, near Station #1	6/5/90	239	Area	16:49	23:21	785	ND

TABLE 4
PERSONAL AND GENERAL AREA AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
JUNE 4-7, 1990

Location	Date	Sample Number	Sample Type	Start (HH:MM)	Stop (HH:MM)	Volume liters	Concentration (ug/M3)
Line 24 Area (SF Gelatin)	6/5/90	240	Area	16:56	23:27	783	68
Packer, Line 24 (SF Gelatin)	6/5/90	241	Personal	16:07	23:09	845	17
Maintenance (Plant Wide)	6/5/90	270	Personal	23:41	05:58	758	7.9
Maintenance (Plant Wide)	6/6/90	300	Personal	08:00	14:48	817	1.2
Maintenance	6/6/90	301	Personal	07:57	14:41	809	ND
Packer, Lines 24 & 25 (SF Gelatin)	6/6/90	302	Personal	07:09	14:34	891	29
Packer, Lines 9 & 10 (S & SF Pudding)	6/6/90	303	Personal	07:04	14:38	909	4.4
Manager, QC Lab	6/6/90	304	Personal	06:18	14:34	993	ND
Fork Truck Operator	6/6/90	305	Personal	06:53	14:25	905	1.1
Packer, Lines 24 & 25 (SF Gelatin)	6/6/90	306	Personal	06:47	14:29	925	16
Packer, Lines 24 & 25 (SF Gelatin)	6/6/90	307	Personal	06:44	14:33	939	32
Operator, Weigh-out Station	6/6/90	309	Personal	06:44	14:49	971	ND
Operator, Weigh-out Station #1	6/6/90	310	Personal	06:46	14:40	949	ND
Operator, Blender # 5	6/6/90	311	Personal	06:55	14:34	919	ND
Operator, Blender # 3	6/6/90	312	Personal	06:51	14:41	941	ND
Technician, QC Lab	6/6/90	313	Personal	07:17	14:56	919	2.2
Packer, Lines 3 & 4	6/6/90	314	Personal	07:10	14:44	909	ND
Operator (float), Line 3	6/6/90	315	Personal	07:06	14:42	913	ND
Fork Truck Operator	6/6/90	316	Personal	06:55	14:32	915	230
Technician, QC Lab	6/6/90	317	Personal	07:03	14:52	939	ND
Packer, Lines 24 & 25 (SF Gelatin)	6/6/90	318	Personal	06:40	14:31	943	16
Weigh-out area	6/6/90	319	Area	07:32	15:16	929	1.1
Operator, Blenders #4 & 8	6/6/90	320	Personal	06:41	14:27	933	ND

TABLE 4
PERSONAL AND GENERAL AREA AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
JUNE 4-7, 1990

Location	Date	Sample Number	Sample Type	Start (HH:MM)	Stop (HH:MM)	Volume liters	Concentration (ug/M3)
Line 24, operator's area (SF Gelatin)	6/6/90	321	Area	07:29	15:19	941	55
Weigh-out area, near hopper 18	6/6/90	322	Area	07:49	14:46	835	9.6
Weigh-out area, near Station #1	6/6/90	324	Area	07:44	14:43	839	9.5
Line 3, Machine 5 area	6/6/90	325	Area	07:38	15:11	907	ND
Weigh-out area	6/6/90	326	Area	16:22	23:15	827	1.2
Weigh-out area	6/6/90	327	Area	16:18	23:26	857	ND
Operator, Line 1	6/6/90	328	Personal	15:43	23:19	913	ND
Fork Truck Operator	6/6/90	329	Personal	16:13	23:24	883	15
Blender (group leader)	6/6/90	330	Personal	16:17	23:21	882	1.5
Packer (SF Gelatin)	6/6/90	331	Personal	15:47	23:07	824	9.7
Packer	6/6/90	332	Personal	16:08	23:13	851	ND
Fork Truck Operator	6/6/90	333	Personal	16:00	23:14	869	1.2
Technician, QC Lab	6/6/90	334	Personal	15:51	23:09	877	ND
Technician, QC Lab	6/6/90	335	Personal	15:58	23:05	855	3.5
Packer (SF Gelatin)	6/6/90	336	Personal	15:48	23:06	877	13
Packer	6/6/90	337	Personal	16:05	23:15	668	4.5
Line 24 area (SF Gelatin)	6/6/90	338	Area	16:28	23:11	807	8.7
Line 3 area	6/6/90	339	Area	16:25	23:20	831	ND
Mechanic (Plant Wide)	6/7/90	400	Personal	08:00	14:16	752	ND
Weigh-out area	6/7/90	401	Area	07:56	14:22	772	3.9
Technician, QC Lab	6/7/90	402	Personal	07:20	14:11	823	2.4
QC Manager	6/7/90	404	Personal	06:24	14:15	943	ND
Packer, Line 4 (S Gelatin)	6/7/90	405	Personal	06:44	14:21	888	ND

TABLE 4
PERSONAL AND GENERAL AREA AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
JUNE 4-7, 1990

Location	Date	Sample Number	Sample Type	Start (HH:MM)	Stop (HH:MM)	Volume liters	Concentration (ug/M3)
Operator (float), Line 3	6/7/90	406	Personal	06:47	14:24	915	ND
Technician, QC Lab	6/7/90	407	Personal	06:49	14:25	913	ND
Operator, Weigh-out Station #4	6/7/90	408	Personal	06:55	14:29	909	2.2
Operator, Blender #5	6/7/90	409	Personal	07:02	14:13	863	ND
Operator, Weigh-out area	6/7/90	410	Personal	06:57	14:43	933	3.2
Operator, Blender #6	6/7/90	411	Personal	07:10	14:09	839	3.6
Operator, Blender #4	6/7/90	412	Personal	07:07	14:18	863	2.3
Packer, Lines 24 & 25 (SF Gelatin)	6/7/90	413	Personal	06:44	14:10	893	11
Fork Truck Operator	6/7/90	414	Personal	06:55	14:07	816	ND
Operator, Lines 24 & 25 (SF Gelatin)	6/7/90	415	Personal	06:47	14:08	830	11
Packer, Line 24	6/7/90	416	Personal	06:45	14:30	931	8.6
Packer, Lines 24 & 25 (SF Gelatin)	6/7/90	417	Personal	06:41	14:12	903	14
Packer (SF Pudding)	6/7/90	418	Personal	07:02	14:17	871	1.2
Line 3 area	6/7/90	419	Area	07:14	14:22	857	ND
Line 24 area	6/7/90	420	Area	07:25	14:13	817	8.6
Weigh-out area	6/7/90	422	Area	07:35	14:20	811	ND
Mechanic	6/7/90	423	Personal	07:12	14:28	628	ND
Lines 9 & 10 general area	6/7/90	426	Area	07:30	14:18	586	ND
Operator (SF Gelatin)	6/7/90	427	Personal	15:08	19:00	464	6.5
Packer	6/7/90	428	Personal	15:11	19:02	462	ND
Operator	6/7/90	429	Personal	15:06	19:11	490	ND
Line 10 area (SF Pudding)	6/7/90	430	Area	15:40	19:20	440	ND
Blending (Group Leader)	6/7/90	431	Personal	15:27	19:00	426	ND
Operator	6/7/90	432	Personal	15:14	19:01	454	ND

TABLE 4
PERSONAL AND GENERAL AREA AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
JUNE 4-7, 1990

Location	Date	Sample Number	Sample Type	Start (HH:MM)	Stop (HH:MM)	Volume liters	Concentration (ug/M3)
Packer	6/7/90	434	Personal	15:14	19:07	466	4.3
Packer, Lines 24 & 25 (SF Gelatin)	6/7/90	436	Personal	15:19	19:04	450	6.7
Technician, QC Lab	6/7/90	437	Personal	15:22	19:01	438	2.3
Line 24 area (SF Gelatin)	6/7/90	438	Area	15:23	19:17	468	13
Fork Truck Operator	6/7/90	440	Personal	15:28	19:23	470	11
Blender #1 area (west wall)	6/7/90	441	Area	15:30	19:09	438	ND
Line 3, Machine 5 area	6/7/90	443	Area	15:37	19:15	436	ND
Fork Truck Operator	6/7/90	444	Personal	17:21	19:03	204	9.8

COMMENTS:

1. There are no specific OSHA, NIOSH, or ACGIH exposure limits for aspartame.
2. * = Sugar-free product.
3. ** = Sugar product.
4. ND = None detected.

TABLE 5
ASPARTAME SAMPLE RESULTS
Full-shift personal samples

OPERATION	(DATE COLLECTED) 1/13/87	1/14/87
WEIGH-OUT	132	151
	40	26
BLENDING	102	55
PACKING	100	70
(OPERATOR)	7	4
PACKING	20	5
(HELPER)	2	ND

(Concentrations shown in micrograms per cubic meter)

TABLE 6
ASPARTAME SAMPLE RESULTS
Short-term personal samples

OPERATION	CONCENTRATION	COMMENTS
WEIGH-OUT	133	Only sugar-free batches
	147	
	432	
BLENDING	140	Only sugar-free batches
	213	
	153	
	197	
OTHER PLANT AREAS	None Detected	Sugar batches

(Concentrations shown in micrograms per cubic meter)

TABLE 7
MEAN, RANGE AND STANDARD DEVIATIONS OF ASPARTAME CONCENTRATIONS
PERSONAL AND GENERAL AIR SAMPLES FOR ASPARTAME
NABISCO BRANDS, INC.
HETA 86-035
SAMPLING CONDUCTED FROM 1986 TO 1990

SURVEY PERIOD	SAMPLES COLLECTED	MEAN (ug/m^3)	RANGE (ug/m^3)	$SD_{(n-1)}$ (ug/m^3)	COMMENTS
January 13 & 14, 1987	24	51 ug/m^3	ND to 545	111	Highest exposures measured during weighing and blending of aspartame into dessert products.
May 5, 1987	37	39 ug/m^3	ND to 432	91	Short-term (approximately 30 minutes) air samples during weigh-out and blending of aspartame measured concentrations up to 432 ug/m^3.
June 4, 1990	32	7 ug/m^3	ND to 37	14	Personal breathing-zone air samples collected on all study participants. Air sampling conducted at both sugar and sugar-free weighing, blending, and packaging operations.
June 5, 1990	41	23 ug/m^3	ND to 301	60	Highest personal exposures occurred at sugar-free weigh-out station and sugar-free gelatin packaging line.
June 6, 1990	38	12 ug/m^3	ND to 230	38	Highest personal exposure occurred on fork-truck driver supplying sugar-free gelatin to packaging line.
June 7, 1990	37	31 ug/m^3	ND to 14	4	Air sampling conducted at both sugar and sugar-free weighing, blending, and packaging operations.

COMMENTS:

1. Both personal breathing-zone and general area air samples were collected during this evaluation. Results from all samples were included in the calculation of the mean, range, and standard deviation.
2. Short-term (approximately 30 minutes) and full-shift personal and area samples were collected. The highest exposures were detected with the short-term air samples which coincided with the handling of aspartame (especially in weigh-out and blending).
3. $SD_{(n-1)}$ = Standard Deviation for sample set.
4. All concentrations are expressed in micrograms of aspartame per cubic meter of air (ug/m^3).
5. There are no specific OSHA, NIOSH, or ACGIH exposure limits for aspartame.

TABLE 8
Demographics of Cases and Controls
Nabisco Brands, Inc.
HETA 86-035

Demographics	14 Controls	17 Cases	Statistical Significance P >
Male	6	4	-
Female	8	13	-
Mean Age	39.5	42.1	0.43
Height (cm.)	172.2	163.7	0.02
Current smokers	10 (66%)	7 (41%)	.07
Mean Years employed	13.6	11.1	0.7

TABLE 9
Prevalence of Symptoms Among Cases and Controls
Nabisco Brands, Inc.
HETA 86-035

Symptom	17 Cases	15 Controls
Chest pain	9 (53%)	2 (13%)
Wheeze	11 (64%)	4 (27%)
Shortness of Breath	8 (47%)	2 (13%)

TABLE 10
Family History of Disease
Nabisco Brands, Inc.
HETA 86-035

Family History of Disease	17 Cases	15 Controls
Hay Fever	6 (35%)	2 (13%)
Eczema	3 (17%)	0
Asthma	7 (41%)	2 (13%)

TABLE 11
Symptom Prevalence of Cases by Smoking Status
Nabisco Brands, Inc.
HETA 86-035

	7 Current Smokers	3 Past Smokers	7 Never Smoked
Chest Pain	5 (71%)	1 (33%)	3 (42%)
Wheeze	7 (100%)	1 (33%)	3 (42%)
Shortness of Breath	4 (57%)	1 (33%)	3 (42%)

TABLE 12
Symptom Prevalence of Controls by Smoking Status
Nabisco Brands, Inc.
HETA 86-035

	10 Current Smokers	3 Past Smokers	2 Never Smoked
Chest pain	2 (20%)	0	0
Wheeze	4 (40%)	0	0
Shortness of Breath	2 (20%)	0	0

TABLE 13
Mean Baseline Pulmonary Function Tests
Nabisco Brands, Inc.
HETA 86-035

Baseline Spirometry tests (Pre-shift)	14 Controls	16 Cases	Statistical Significance P >
Mean FVC percent predicted*	98% (range 70-124%)	99% (range 59-125%)	0.73
Mean FEV_1 Percent Predicted*	93% (range 67 - 115%)	95% (range 50 - 120%)	0.66
Mean FEV_1/FVC Percent Predicted	95.9% (range 65-107)	95.2% (range 85-103	0.92

* Predicted values from Knudson, et al., Am Rev Respir Dis 1983.

TABLE 14
Mean Cross-Shift Pulmonary Function Tests
Nabisco Brands, Inc.
HETA 86-035

Pulmonary Function	Controls (n=14)	Cases (n=16)	P >
Cross-shift change FEV_1 *(in liters)*	0.04	0.09	0.36
Cross-shift change FVC *(in liters)*	0.01	0.02	0.87
Percent Change in cross-shift FEV_1	0.85% (range -7.6% to +11.9%)	3.49% (range -9% to +20%)	0.34

TABLE 15
Mean Cross Work-Shift Pulmonary Function Test Results
For Cases and Controls With Aspartame Exposure*
On the Day of their Spirometry
Nabisco Brands, Inc.
HETA 86-035

Pulmonary Function	Controls (n=6)	Cases (n=12)	P >
Cross shift change FEV_1 *(in liters)*	0.10	0.12	0.80
Cross shift change FVC *(in liters)*	0.00	0.05	0.50
Percent Change in cross-shift FEV_1	3.54% (range -7.7% to -0.5%)	3.99% (range -9% to +20%)	0.91

* By personal breathing-zone air sampling.

APPENDIX I

CHRONOLOGY OF EVENTS
NABISCO BRANDS, INC.
SEVILLE, OHIO

1. An initial Health Hazard Evaluation (HHE) request, submitted by the United Food and Commercial Workers (UFCW) Union Local 880 on October 25, 1985, concerned irritation of the nose, throat, and skin allegedly from aspartame (*Nutrasweet®*) exposure.

2. The HHE request was assigned to NIOSH investigators on October 31, 1985, and initial contact was made with the requester (Business Agent for UFCW Local 880) on November 8, 1985.

3. The Seville plant manager was contacted on November 15, 1985. An opening conference was tentatively scheduled on November 20, 1985; however, this initial site visit was eventually delayed until February 5, 1986 for legal reasons following discussions with the Manager, Safety and Health Group, Regulatory Compliance Engineering, Nabisco. The Nabisco Corporation was concerned with the merit of the HHE and the potential impact on trade secret processes.

4. Based on information gathered before the initial visit, the HHE program requested, on December 18, 1985, that the NIOSH Division of Physical Science and Engineering develop a field method for collecting air samples for aspartame, a dipeptide methyl ester.

5. The air sampling method (See Appendix II for a detailed discussion of the sampling and analytical method) was completed in September 1986. A follow-up survey to the Seville plant, planned for December 2-5, 1986, was delayed at the request of Nabisco's corporate safety and health office, until January 12 to 15, 1987. The delay was to allow Nabisco additional time to arrange side-by-side sampling. The NIOSH method for air sampling for aspartame was supplied to Nabisco personnel prior to this follow-up survey. There was no medical component in this follow-up survey and the primary intent of this visit was to determine if aspartame levels were measurable.

6. A follow-up visit, conducted by NIOSH investigators on May 5, 1987, included both personal breathing-zone and general area air sampling and administration of 158 screening questionnaires to all available plant employees. The air samples were collected for aspartame in both sugar and sugar-free dessert operations. The questionnaire survey covered all three shifts and included hourly and salaried employees.

7. Air sampling results from these two surveys were summarized in letters, dated March 27, 1987, and June 26, 1987, respectively, to Nabisco and UFCW

Local 880. The results of the screening questionnaire identified over 35 workers with symptoms compatible with occupationally asthma. Twenty-one employees were subsequently contacted and interviewed over the telephone by NIOSH investigators between July 1987, and January 1988.

8. Based on the results from the 1987 questionnaire and the telephone interviews, NIOSH investigators developed a medical protocol to determine if some workers at the Seville plant had developed asthma as a result of working with, and having been exposed to, aspartame. The medical protocol received approval from the NIOSH Human Subjects Review Board on September 9, 1988. Nabisco was notified by letter in September 1988, of plans to collect further medical and environmental data on symptomatic workers and a suitable number of non-symptomatic employees. A copy of the medical protocol was provided to Nabisco representatives.

9. At the request of Nabisco management, a meeting was held at NIOSH in Cincinnati (on November 18, 1988), which was attended by representatives of Nabisco and UFCW Local 880. The intent of this meeting was to discuss the medical protocol and schedule the follow-up site visit. Internal and outside legal counsel for Nabisco attending this meeting raised several issues, including the company's potential liability arising from the proposed medical tests and the refusal by NIOSH to take measures over and above existing safeguards to protect Nabisco from such liability.

10. Nabisco, in a letter dated December 19, 1988, stated that the company would not voluntarily provide NIOSH investigators access to their facilities.

11. NIOSH obtained an warrant on April 25, 1989, from the U.S. District Court for the Northern District of Ohio. The warrant was served to Nabisco management in Seville, Ohio at 1:59 p.m. that same day.

12. On April 26, 1989, Nabisco Brands, Inc. filed a Motion to Quash the inspection warrant with the U.S. District Court for the Northern District of Ohio. As a result, the environmental and medical follow-up at the Seville plant was delayed pending resolution of this motion.

13. On November 15, 1989, NIOSH obtained from the U.S. Magistrate a favorable decision which denied Nabisco Brands, Inc. Motion to Quash.

14. On November 30, 1889, Nabisco Brands, Inc. filed an appeal of the Magistrate's decision. On March 22, 1990, the U.S. District Court upheld the Magistrate's decision and denied Nabisco Brands, Inc. Motion to Quash the warrant.

15. The final follow-up environmental and medical evaluation was conducted by NIOSH investigators at the Seville plant on June 4 to 7, 1990.

APPENDIX II

SAMPLING AND ANALYTICAL METHOD FOR WORKPLACE MONITORING OF ASPARTAME IN AIR

WILLIAM N. ALBRECHT[A] AND GREGORY A. BURR[B] AND CHARLES E. NEUMEISTER[C]

Industrial Analytical Laboratory, Inc. 3615 Harding Avenue, Honolulu, HI 96816[A];
National Institute for Occupational Safety and Health, 4676 Columbia Parkway,
Cincinnati, Ohio 45226, Division of Surveillance, Hazard Evaluations, and Field Studies[B]
and Division of Physical Science and Engineering[C]

ABSTRACT

Aspartame™ (L-aspartyl-L-phenylalanine methyl ester; Nutrasweet®; Nutrasweet Company, Chicago, Illinois) is a dipeptide methyl ester that imparts a sweet taste sensation. It has been approved for use in the United States since 1981. In the course of a National Institute for Occupational Safety and Health (NIOSH) study to examine potential worker health effects at a food plant in the U.S., a method for sampling aspartame in air and its analysis, was developed. A walk-through survey of the abovementioned plant identified potential aspartame exposures to employees during weighing, blending, and packaging of dry dessert mixes. Potential analytical interferences included: sodium citrate, ascorbic and fumaric acids, gelatin, maltodextrin, and mannitol.

The collection system, using portable high flow [1 to 5 liters per minute (Lpm)] air pumps, is suitable for personal and area air sampling in industrial settings. Samples were collected on 1.0 micron pore size, 37 millimeter diameter polytetrafluoroethylene (PTFE) filters with a polyethylene backing. Analysis was by high pressure liquid chromatography.

Laboratory experiments and field testing demonstrated excellent recovery of aspartame from PTFE filters. It was also found that aspartame does not migrate or decompose on the filter during sampling, or when stored at ambient temperature for one month. No special precautions are necessary for either sample collection or transportation to the analytical laboratory.

Possible interferences from food additives, which were collected along with aspartame during actual field sampling, were absent. The effect of humidity extremes on sampling and subsequent measurement was not evaluated. With minor modifications, this method should be applicable to sampling most dipeptides in air.

INTRODUCTION

Several dipeptides (two covalently-bonded amino acids) possess properties which impart a taste sensation indistinguishable from salt or sugar. For example, ornithyltaurine tastes as salty as sodium chloride but is not, as yet, commercially available.[1] Aspartame™ (L-aspartyl-L-phenylalanine methyl ester), better known by the tradename Nutrasweet®, is approximately 180 times as sweet as sucrose and has been approved for use in this country since 1981.[2] Previously, health hazards from the ingestion of aspartame have centered on risks to phenylketonurics (individuals who do not properly metabolize phenylalanine), and the potential for aspartame to increase the level of excitatory neurotransmitters in the brain. The former has been satisfactorily resolved by requiring a warning label to appear on all products containing aspartame. The latter remains a point of controversy.[3,4] An individual has presumptively demonstrated an immune response (urticaria) after ingestion.[5]

Workers engaged in the manufacture or blending of aspartame are conceivably exposed, by inhalation, to doses many times greater than the general public if adequate engineering controls are not in place. The possible role of aspartame in the genesis of occupational asthma is as yet unclear even though studies have shown that it was not a direct mast cell or basophil secretogogue in vitro, or in vivo as assessed by skin testing.[6] In addition, during acute incubation, aspartame did not affect IgE-mediated histamine release from mast cells. Inconsistencies remain, however, since aspartame or it's diketopiperazine derivative (DKP), a spontaneous decomposition product, approximately 2% by weight in the final aspartame product), can presumably act as antigen, and DKP has not yet been specifically examined for antigenic properties.[5]

In the course of evaluating potential health hazards to workers engaged in the blending of aspartame at a food plant that packages dry, sugar-free dessert products, and in anticipation of evaluating other dipeptide exposures in the future, researchers from NIOSH developed a sampling and analytical method for aspartame in air. This method, a modification of an existing high-performance liquid chromatography (HPLC) assay of aspartame and it's precursors and decomposition products, only addresses aspartame.[7] A walk-through survey of the abovementioned food plant identified potential aspartame exposures to employees during weighing, blending, and packaging of dry dessert mixes. Potential analytical interferences included: sodium citrate, ascorbic and fumaric acids, gelatin, maltodextrin, and mannitol.

Please note that the mention of trade names or products does not constitute endorsement by NIOSH.

MATERIALS AND METHODS

L-aspartyl-L-phenylalanine methyl ester (99.9% pure; Molecular weight 294.3; melting point 248-250°C), was purchased from the Aldrich Chemical Company (Milwaukee, Wisconsin) for use in all experiments and as standards for the calibration curve. The sampling medium used was a Millipore "Fluoropore" polytetrafluoroethylene (PTFE) filter. These filters have a polyethylene backing, a pore size of 1.0 micron, and a diameter of 37 millimeters (mm). PTFE filters are extremely inert and can accommodate a maximum flowrate of 18 Lpm without appreciable pressure drop which could affect the performance of the air sampling pump. The entire sampler, consisting of a filter and cellulose backup pad, is placed within a two-piece plastic cassette.

The HPLC system used for measurement consisted of a Waters model 720B autosampler, two 6000A pumps, a 760 system controller, and a C_{18} Radial Compression Column in a Radial Compression Module, with a Kratos Spectroflow 783 Programmable Absorbance Detector set at 220 nanometers (nm). A Hewlett-Packard Model 3357 Laboratory Automation System completed the system. The isocratic mobile phase was 60% eluent A: 2.062 g 1-heptanesulfonic acid sodium salt (Fisher Chemical Co., Cincinnati, Ohio) and 0.45 g monobasic potassium phosphate (Aldrich Chemical Co., Milwaukee, WS) in 1 L distilled water (pH adjusted, purged, and degassed); and 40% eluent, B: 2.062 g of 1-heptanesulfonic acid sodium salt in 1 L of 3:2 acetonitrile-water. The flowrate was 1 mL per minute with an injection volume of 25 microliters (uL).

Since personal as well as area air samples were to be collected, the sampling system was tested using SKC Model 224 Universal sampling pumps calibrated at 2.5 Lpm. Similar high-flow air pumps, however, would be adequate for this sampling method. A total sampling volume of 1000 L was tested.

A calibration curve ranging from 0.5 to 463 ug/mL of aspartame was prepared. A typical calibration curve with 95% confidence limits is shown in Figure 1. Stock solution was made by dissolving 0.05 g of aspartame in 10 mL of extraction solution (eluent B). Serial dilution of this stock with additional eluent B was used to prepare the calibration standards.

For sample preparation, the PTFE filters were removed from the cassettes in the laboratory and placed into 20 mL vials; the back-up pads were discarded. Two mL of extraction solution (eluent B) were added to each vial.

Known masses of aspartame were required to evaluate extraction efficiency and sample

stability. A standard working solution was made by dissolving a known amount of aspartame in methanol. A total of twenty-seven filters was prepared using this technique, and all 27 were analyzed, in triplicate, to evaluate the overall amount recovered. Four concentration levels, over the range of two orders of magnitude, were used in these evaluations: 435.4, 217.7, 43.5, and 4.35 ug per filter. The standard solution was applied, via syringe, to the PTFE filters and the methanol allowed to evaporate.

Both static and dynamic extraction efficiency for aspartame on PTFE filters was determined. Static extraction efficiency was measured by spiking 3 filters at each of the 4 concentration levels, allowing the methanol to evaporate, and then extracting the filters with eluent B. Dynamic extraction stability was measured by drawing 1000 L of room air through 12 identically spiked filters to ascertain if migration or decomposition of aspartame occurred during simulated sampling, and then proceeding as with the measurement of static efficiency. The storage stability of aspartame was measured by spiking each of three filters with 43.5 ug of aspartame, then placing the closed cassettes on a laboratory benchtop, at ambient temperature (23.3°C), for one month without drawing air through them.

RESULTS AND DISCUSSION

Regression analysis of the calibration curve data indicated a limit of detection (LOD) of 2 ug per filter with a limit of quantitation (LOQ) of 7 ug per filter. The results of the static and dynamic stability at four filter loading levels are presented in Figure 2. Table I contains the data on which this bar graph is based.

For the twelve filters prepared for the static extraction efficiency experiment, the mean percent recovery over four filter loading levels was 99.5% ± 2.1% with a range of 94.5-101.8%. The dynamic extraction efficiency experiment was found to be 101.3% ± 2.9% over the range of 97.7-109.2%. The three filters prepared at 43.5 ug/filter and evaluated for storage stability after one month showed a mean of 101.8% ± 2.7% with a range 98.6-103.9%.

To compute the overall extraction efficiency, the data obtained were normalized to complete recovery, and from the analysis of 27 spiked samples, an average recovery of 1.005, with a relative standard deviation (S_R) of 0.026, was obtained (overall precision criteria stipulates that pooled S_R should be less than 0.105).[7] The range was 1.092 to 0.945.

Sixty-six personal and area samples were collected using this method during a health hazard evaluation of aspartame exposure at a commercial food packaging plant. A walk-through survey of the facility identified potential aspartame exposures to employees during weighing, blending, and packaging of dry, sugar-free dessert mixes. After sampling, the

filters were transported to the analytical laboratory with no special precautions. As shown in stability studies, pure aspartame samples may be stored for up to one month with no migration or decomposition of the collected aspartame.

In the first of two field studies at this plant, fumaric acid, sodium citrate, and ascorbic acid were chromatographically separated from aspartame with retention times of approximately 2 minutes, compared to 12.5 minutes for aspartame. Sampling and recovery of aspartame under these conditions were not affected. A copy of a typical field sample chromatogram is shown as Figure 3. At the onset of these field sample analyses, the following method modifications were made:

1. The extraction volume was increased from 2 to 4 mL due to the large amount of material on the PTFE filters.

2. An increase in sample response of aspartame was obtained by using an absorbance maximum of 211 nm for quantitation instead of 220 nm.

Analyses of samples from the second field study showed a LOD of 2 ug/filter and a LOQ of 5 ug/filter. The lower LOQ is attributed to the smaller signal-to-noise ratio exhibited by the HPLC during the analysis. All samples from this determination were run in duplicate and agreement between the two was within 6%. Tables II, III, and IV summarize the results of air sampling for aspartame conducted in this plant study.

CONCLUSIONS

This study demonstrated excellent recovery of aspartame from PTFE filters. It was found that aspartame does not migrate or decompose on the filter during sampling, or when stored at ambient temperature for one month. This method complies with the portion of the NIOSH standards completion criteria requiring greater than or equal to 90% recovery of sample from media.[8] No special precautions are necessary for either sample collection or transportation to the analytical laboratory.

The collection system, using portable high flow (1 to 5 Lpm) air pumps, is suitable for personal and area air sampling in industrial settings. Food additives, such as flavorings ("artificial flavors"), stabilizers (ascorbic acid), and food colors (e.g., FD&C yellow #5), which were incorporated into the various dessert products and collected along with aspartame during actual field sampling, were shown not to affect the analysis. The effect of humidity extremes on sampling and subsequent analysis was not evaluated. With minor modifications, this method should be applicable to sampling most dipeptides in air.

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Table I
Extraction and Stability Studies of Aspartame

Sample	Sample Spiked in ug/filters[a]	Amount Recovered in ug/filter	% Recovery	% RSD[b]
F1	435.4	445.8	102.3	
F2	435.4	434.6	99.8	
F3	435.4	439.0	100.8	
AVG(F)	435.4	439.8	101.0	1.3
A1	435.4	438.3	100.7	
A2	435.4	443.1	101.8	
A3	435.4	433.2	99.5	
AVG(A)	435.4	438.2	100.6	1.2
AVG(F+A)	435.4	439.0	100.8	1.1
F4	217.7	221.6	101.8	
F5	217.7	221.7	101.8	
F6	217.7	214.9	98.7	
AVG(F)	217.7	219.4	100.8	1.8
A4	217.7	221.5	101.7	
A5	217.7	220.6	101.3	
A6	217.7	212.2	97.4	
AVG(A)	217.7	218.1	100.2	2.4
AVG(F+A)	217.7	218.8	100.5	1.9
F7	43.5	44.3	101.8	
F8	43.5	47.5	109.2	
F9	43.5	43.4	99.8	
AVG(F)	43.5	45.1	103.6	4.8
A7	43.5	41.1	94.5	
A8	43.5	43.6	100.2	
A9	43.5	42.9	98.6	
AVG(A)	43.5	42.5	97.7	3.1
ST1	43.5	42.9	98.6	
ST2	43.5	44.7	102.8	
ST3	43.5	45.2	103.9	
AVG(ST)	43.5	44.3	101.8	2.7
AVG(F+A+ST)	43.5	44.0	101.1	4.1
F10	4.4	4.3	97.7	
F11	4.4	4.5	102.3	
F12	4.4	4.4	100.0	
AVG(F)	4.4	4.4	100.0	2.3
A10	4.4	4.3	97.7	
A11	4.4	4.4	100.0	
A12	4.4	4.4	100.0	
AVG(A)	4.4	4.4	100.0	1.3
AVG(F+A)	4.4	4.4	100.0	1.7

Comments:

F - Static Extraction efficiency samples (no air drawn through the spiked filter).

A - Dynamic extraction efficiency samples (1000 liters of air drawn through each spiked filter).

ST- 30 day passive stability test of pure aspartame on filter.

[a] Micrograms of aspartame per filter.

[b] Relative standard deviation.