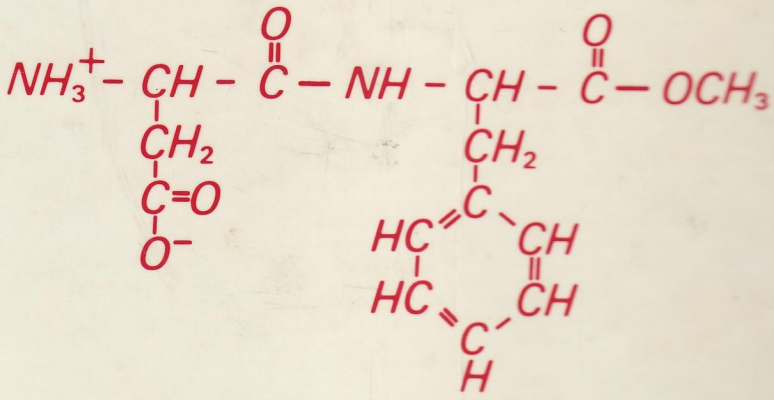
ASPARTAME

Physiology and Biochemistry

edited by

Lewis D. Stegink • L. J. Filer, Jr.



about the book . . .

This unique volume inaugurates a totally new phase in the study of chemical structure in relation to taste, and establishes a model for future food additive studies.

Aspartame addresses five major issues: history and development . . . metabolism of aspartame's component parts . . . sensory and dietary aspects . . . preclinical studies in animals . . . and aspartame metabolism in humans. The volume examines specific topics arising from human consumption, including aspartame ingestion during pregnancy, and use by diabetics and individuals heterozygous for phenylketonuria. The chapters discuss investigations of possible behavioral effects, and studies evaluating possible neurotoxicity and neuropathology.

Look to this authoritative sourcebook first for a truly informed perspective! *Aspartame* serves as an unequaled reference for nutritionists, food scientists, toxicologists, biochemists, dieticians, taste physiologists, physicians, dentists, and consumer groups.

about the editors . . .

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nd Textbooks

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L.J. Filer, Jr.
University of Iowa
College of Medicine
Iowa City, Iowa

1984

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Contents

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Methanol Metabolism and Toxicity

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INTRODUCTION

Methanol is commonly used in industry for organic synthetic procedures or as a solvent. As a result, it is accessible to the general public in a variety of products such as antifreeze, fuels (Sterno), duplicating machine fluids, and in gasoline as a fuel extender. Methanol and other alcohols have been employed as sources of energy or fuel for many years, particularly in times of war. Methanol's use as an automobile fuel, as well as other proposed uses for energy production, will increase human methanol contact from a limited laboratory or industrial exposure to a general environmental exposure. Although methanol theoretically represents a "clean" substance capable of oxidation to water and carbon dioxide, in humans biochemical reactions produce metabolites that are clearly toxic.

A consideration of the toxicity of methanol, especially in species which demonstrate signs and symptoms, seems appropriate for several reasons. First, humans are sensitive to methanol poisoning, and limits of tolerance must be considered. Second, nutritional factors may play an important role (e.g., folate deficiency) in determining susceptibility. Our current understanding of the mechanisms involved in methanol toxicity is described.

CHARACTERISTICS OF POISONING IN MAN

The toxicity of methanol in humans has been appreciated since the early part of the twentieth century. In 1855 MacFarlan (1) proposed that a mixture of 1 part

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Projected Aspartame Intake: Daily Ingestion of Aspartic Acid, Phenylalanine, and Methanol

Roberta Roak-Foltz and **Gilbert A. Leveille**
General Foods Corporation, White Plains, New York

The safety assessment of any food additive requires a knowledge of the pharmacology and toxicology of the additive and information regarding exposure. Population exposure is generally difficult to determine for a new compound and cannot be accurately established before its introduction. For this reason it is important to ensure that estimates of exposure be conservative. Usually this means consciously overestimating rather than underestimating intake exposure.

Elsewhere in this volume there is extensive discussion of the metabolism and toxicology of aspartame and its degradation products phenylalanine, aspartic acid, methanol, and diketopiperazine. These extensive studies demonstrate that high doses of aspartame are well tolerated. However, it is important to estimate the probable range of aspartame intake that might be anticipated.

We have used two approaches to estimate exposure to aspartame or its metabolites. The simplest involved the assumption that aspartame would replace the apparent per capita sugar intake. The per capita caloric sweetener intake was calculated, on the basis of disappearance, to be 156 g/day (1). Using a sweetener ratio of 180:1, this yields a daily estimated aspartame intake of 867 mg/day. Actual intake would be somewhat lower, since it is recognized that disappearance data overestimate consumption and not all of the sweetener applications can be replaced by aspartame.

The second approach used to project aspartame intake involved developing a menu containing generous amounts of added sugars and assuming the substitution of aspartame for the added sweeteners. This menu is shown in Table 1. In Table 2

Table 1 Daily Menu Used to Estimate Potential Aspartame Intake

Meals	Snacks
Breakfast	
6 fl oz breakfast beverage[a]	
1 oz sugar-sweetened cereal[a]	
½ banana	
½ cup milk	
1 slice toast	
1 teaspoon margarine	
1 cup coffee	
3 packets sugar[a]	1 fresh apple
Lunch	
½ cup pea soup	
1 sandwich	
3 slices bologna	
1 oz cheddar cheese	
2 slices bread	
1 teaspoon mustard	
2 lettuce leaves	
1½ oz potato chips	
8 fl oz soft drink[a]	2 sticks chewing gum[a]
½ cup vanilla pudding[a]	8 fl oz soft drink[a]
Dinner	
1 fried chicken leg	
½ cup peas and carrots	
½ cup mashed potatoes	
1 slice bread	
1 teaspoon margarine	
1 cup milk	
½ cup gelatin dessert[a]	
1 peach half	
2 tablespoons whipped topping[a]	
1 cup tea	
2 packets sugar[a]	8 fl oz soft drink[a]

[a]Foods and beverages in which aspartame could substitute for sucrose or corn sweeteners.

are shown the calculated values for the menu containing sweeteners or aspartame. This menu provided 2800 kcal and 260g of total sugars. Of this amount, 190 g was added sugar which conceivably could be substituted by aspartame. Using the 180:1 ratio of aspartame sweetness to sucrose sweetness, total substitution would result in a daily intake 1056 mg of aspartame. However, the sweetness ratio varies

Table 2 Nutrients Provided by Menu Added Sweeteners by Aspartame

	Menu with sucrose
Energy	2800 kcal
Protein	86 g
Carbohydrate	396 g
Total sugars	261 g
Phenylalanine	4.0 g
Aspartic acid	7.3 g
Methanol	–

from product to product. This menu
the level typical for each product app
containing foods.

Both of these approaches yield sim
used to estimate the phenylalanine, a
metabolism of aspartame yields, on a
alanine, 40% aspartic acid, and 10% m
typical aspartame level for each food
result in 10 and 4% increased intakes
tively, and an added methanol exposu

On the basis of disappearance data
of 867 mg would translate to an increa
alanine, 347 mg of aspartic acid, and
phenylalanine and aspartic acid daily
as part of the 1977-1978 U.S. Departm
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(e.g., corn, oats, rice, wheat for cerea
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aspartic acid intake by 5% and would

It is clear from these estimates that
intake appreciably. Similarly, the add
anol, which is formed by enzymatic sp

ıtial Aspartame Intake

Snacks

1 fresh apple

2 sticks chewing gum[a]
8 fl oz soft drink[a]

3 fl oz soft drink[a]

substitute for sucrose or

containing sweeteners or aspartame.
total sugars. Of this amount, 190 g
substituted by aspartame. Using the
e sweetness, total substitution would
. However, the sweetness ratio varies

Table 2 Nutrients Provided by Menu Before and After Replacement of Added Sweeteners by Aspartame

	Menu with sucrose	Menu with aspartame	Percent difference
Energy	2800 kcal	2200 kcal	−21
Protein	86 g	88 g	+2
Carbohydrate	396 g	225 g	−43
Total sugars	261 g	71 g	−73
Phenylalanine	4.0 g	4.4 g	+10
Aspartic acid	7.3 g	7.6 g	+4
Methanol	–	75 mg	–

from product to product. This menu provides about 750 mg of aspartame when the level typical for each product application is used for the potential aspartame-containing foods.

Both of these approaches yield similar values for aspartame intake and can be used to estimate the phenylalanine, aspartic acid, and methanol exposures. The metabolism of aspartame yields, on a weight basis, approximately 50% phenylalanine, 40% aspartic acid, and 10% methanol. Using the menu approach and the typical aspartame level for each food, the estimated intake of aspartame would result in 10 and 4% increased intakes of phenylalanine and aspartic acid, respectively, and an added methanol exposure of 75 mg.

On the basis of disappearance data, the estimated potential aspartame intake of 867 mg would translate to an increased daily consumption of 433 mg of phenylalanine, 347 mg of aspartic acid, and 87 mg of methanol. For comparison, the phenylalanine and aspartic acid daily intakes were estimated from data collected as part of the 1977-1978 U.S. Department of Agriculture Nationwide Food Consumption Survey (2). Amino acid levels were calculated for the average amount consumed for each of the 44 food groups reported in the survey. When a group represented several foods with different amino acid levels, an average was used (e.g., corn, oats, rice, wheat for cereal grains) or one form was selected as representative (e.g., chicken broiler or fryer, flesh only, roasted for all chicken).

Household measure equivalents were determined for the foods from the 44 groups using weights and measures from the U.S. Department of Agriculture (3-10). For this purpose the 44 groups were collapsed into 17 categories (Table 3). This approach yielded estimates of 3.6 and 6.8 g for daily phenylalanine and aspartic acid intakes, respectively. Combining these data, replacement of all sweeteners with aspartame would increase phenylalanine intake by 12% and aspartic acid intake by 5% and would add 87 mg of methanol to the diet.

It is clear from these estimates that aspartame is not likely to alter amino acid intake appreciably. Similarly, the added methanol burden is insignificant. Methanol, which is formed by enzymatic splitting of pectic substances, is a component

Table 3 Average Intake per Individual in a Day

6.7 oz	Meat, poultry, or fish
1½ cups	Milk
½ oz	Cheese
½	Egg
1 oz	Legumes, nuts, or seeds
Equivalent of 4 slices	Bread (includes other baked goods)
½ oz	Ready-to-eat cereal
½ cup	Pasta or other grain mixtures
½	Potato
1 cup	Vegetables
½ cup	Fruit or fruit juice
2 teaspoons	Table fat or salad dressing
1 cup	Soft drinks or fruit drinks
¼ cup	Beer or ale
Equivalent of 2 tablespoons	Sugar, candy, or other sweets
1½ cups	Coffee (6 fl oz cup)
2/3 cup	Tea (6 fl oz cup)

Source: Adapted from *The USDA Nationwide Food Consumption Survey 1977-78, Preliminary Report* No. 2, Food and nutrient intakes of individuals in 1 day in the United States, Spring 1977, Tables 1.1a, 1.2a, 1.3a, 1.4a, and 1.5a.

of many fruits, vegetables, and wines. The amount of methanol contributed by these foods in the course of a day would likely exceed any contribution from aspartame (11-17).

It should be emphasized that these estimates are by design high. Actual intakes of aspartame will certainly be less, probably closer to 50% of the values we have estimated.

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Aspartame Metabolism in Humans: Acute Dosing Studies

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Toxicology is based on the premise that all compounds are toxic at some dose. Salt, water, sugar, and even a mother's love produce deleterious effects when given in inappropriate amounts. Thus it is not surprising that very large doses of aspartame (Fig. 1) or aspartame's component parts (aspartate, phenylalanine, and methanol) produce deleterious effects in sensitive animal species. The critical question is whether the compound is potentially harmful at normal use and potential abuse levels.

Aspartame may be absorbed and metabolized in one of two ways (Fig. 2). It may be hydrolyzed in the intestinal lumen to aspartate, phenylalanine, and methanol by proteolytic and hydrolytic enzymes (1-5). These compounds are absorbed from the lumen and reach the blood in a manner similar to that of amino acids and methanol arising from dietary protein or polysaccharides. Alternatively, aspartame may be absorbed directly into mucosal cells by peptide transport mechanisms (4,5) with subsequent hydrolysis within the cell to aspartate, phenylalanine, and methanol. In either case, large doses of aspartame release aspartate, phenylalanine, and methanol to the portal blood, and these components must be metabolized and/or excreted.

Olney (6-9) and Reif-Lehrer (10) expressed concern about the safety of aspartame because of its aspartate content. Administration of high doses of aspartate to neonatal mice or rats results in elevated plasma aspartate concentrations (11-16) and hypothalamic neuronal necrosis (14-18). Aspartame administered in large amounts (1-2.5 g/kg body weight) to infant mice produces neuronal necrosis