

# Straight Facts About Aspartame & Other Low-Calorie Sweeteners

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**Toxicologist Bernadene Magnuson, PhD\***

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\*The opinions expressed by the speakers are their own and do not necessarily reflect the positions or opinions of The Coca-Cola Company. \_



**Dr. George L. Blackburn, MD, PhD**

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## Expert Review of The Safety of Aspartame



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# Expert Review of the Safety of Aspartame

Bernadene Magnuson, Ph.D.

## Expert Panel

William J. Waddell, M.D., Chair

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Ron Walker, Ph.D.

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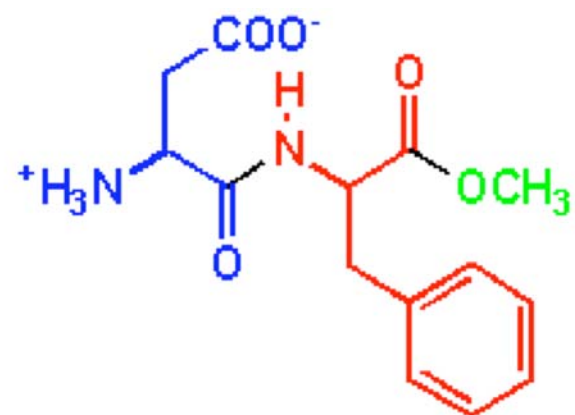
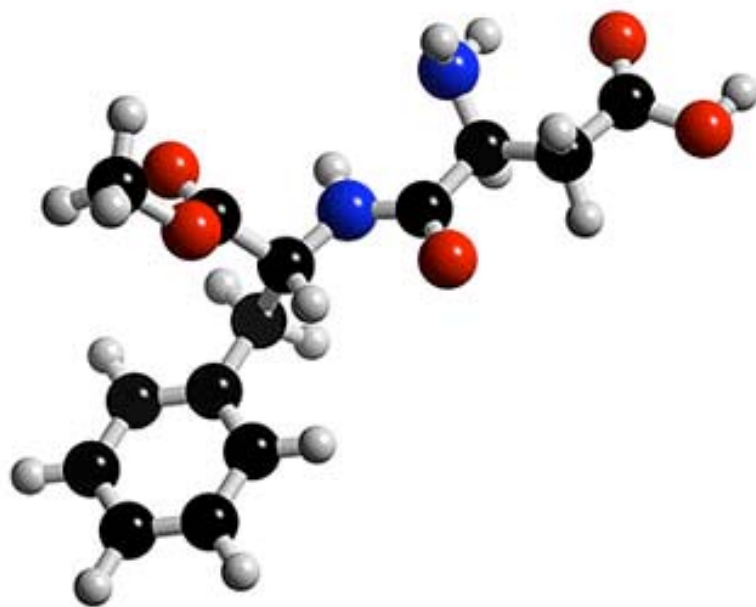


## Low-Calorie Sweeteners



- Questions regarding the safety of aspartame have continued to surface in the press and internet
- Recent lifetime exposure studies also brought aspartame safety into question
- Goal = convene an independent international panel of toxicology experts to review all scientific studies and assess the **safety of current consumption** of aspartame

# Aspartame



Aspartyl-phenylalanine methyl ester

<http://www.3dchem.com/>

## Aspartame Stability

- Can breakdown
    - with long term storage
    - conditions high temperature and high pH
  - Breakdown products
    - Aspartylphenylalanine (dipeptide)
    - Diketopiperazine (DKP) (cyclic dipeptide)
    - Methanol
    - Aspartate and phenylalanine
  - Breakdown product safety also evaluated
- } **Not Sweet**

# Premarket Safety Evaluation

- To support aspartame safety, comprehensive battery of studies were conducted
  - Acute, Sub-chronic, Long-term toxicity
  - Carcinogenicity
  - Genetic toxicity
  - Reproductive toxicity
  - Teratogenicity
  - Also human studies – blood chemistry, diabetics, children
- Data reviewed by every major international food authority (FDA, Health Canada, EU, JECFA, etc.)
- Approved in over 130 countries

## Aspartame ADI Values

- Acceptable Daily Intake (ADI) = amount considered safe to consume every day for a life time without adverse effects
  - DOES NOT mean that consumption greater than ADI will have any effect because of conservative nature
- ADI is set by
  - determining the amount animals can consume every day without effect = No-Observed Effect Level (NOEL)
  - Then apply “**safety factors**” to account for
    - differences between individuals (10 X)
    - differences between humans and animals (10 X)
- NOEL/safety factors = ADI
- **FDA has set the ADI at 50 mg/kg body wt**

## Number of Servings/day to reach ADI (50 mg/kg body weight)

<b>Food/Beverage</b>	<b>Adult (150 lb.)</b>	<b>Child (50 lb.)</b>
Carbonated soft drink (12 oz.)	20	6
Powdered soft drink (8 oz.)	33	11
Gelatin (4 oz.)	42	14
Tabletop sweetener (packet)	97	32

## Applications/Use of Aspartame

- Carbonated soft drinks
- Juices
- Puddings, fillings, jellies
- Desserts and toppings
- Table-top sweeteners (tablets and powders)
- Chewing gum
- Fruit preserves
- Bread spreads
- Frozen desserts
- Dairy products
- Jams, marmalades
- Breakfast cereals
- Confectionery
- Hot chocolate drinks
- Multivitamins
- Micro breath mints
- Personal care products, pharmaceuticals

## The Process-Literature

- Scientific literature databases
- FDA Federal Register
- Unpublished regulatory submission reports
- National Toxicology Program studies
- Selection of studies
  - Over 500 articles cited in this report
  - Elimination criteria
    - Research on sensory and/or product applications
    - Investigating potential health benefit

## The Process - Consumption

- Analysis of current consumption of aspartame
  - Proprietary method of analysis (Burdock Group)
  - Food intakes from National Health and Nutrition Examination Survey (NHANES) 2001-2002, USDA.
  - Levels of aspartame content in foods
    - Typical use levels from industry
    - Levels reported in literature
    - Assumptions included all artificial sweetener were aspartame, highest level reported used as default

## NHANES-Based Estimate of Aspartame Consumption

Values for users only	mg/kg bw/day
50 <sup>th</sup> Percentile (Mean)	4.8
90 <sup>th</sup> Percentile	10.4
95 <sup>th</sup> Percentile	13.3

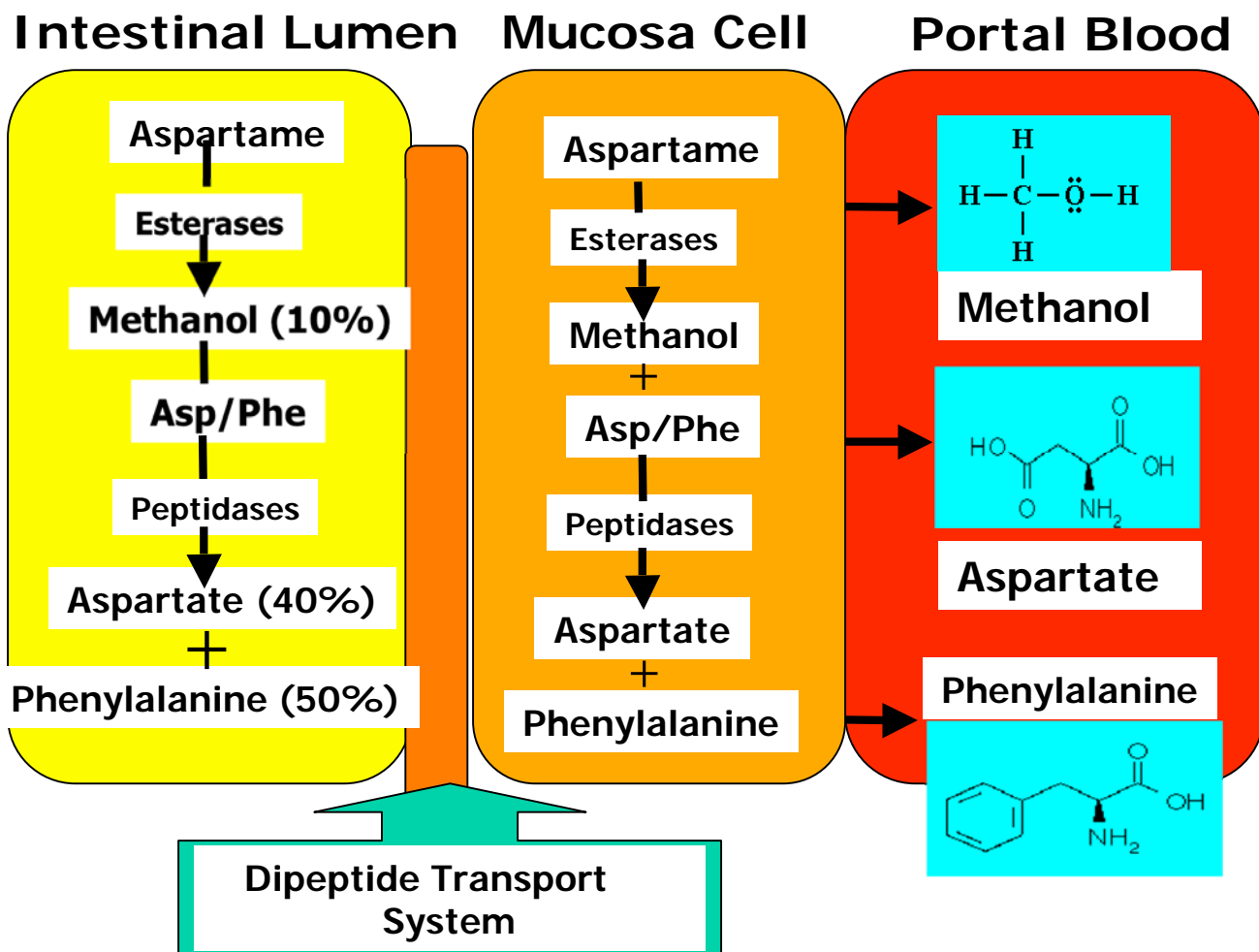
**Acceptable Daily Intake = 50 mg/kg bw/d**

ADI level = considered safe to consume every day for life

## Consumption of Aspartame

- The intake of aspartame has increased in recent years; the change is not dramatic
- Remains well below the ADI even for high intake subpopulations
- NHANES over-estimation; assumptions
- Worst-case scenario predictions suggest chronic intakes will not reach the ADI

# Aspartame Absorption in the Gut

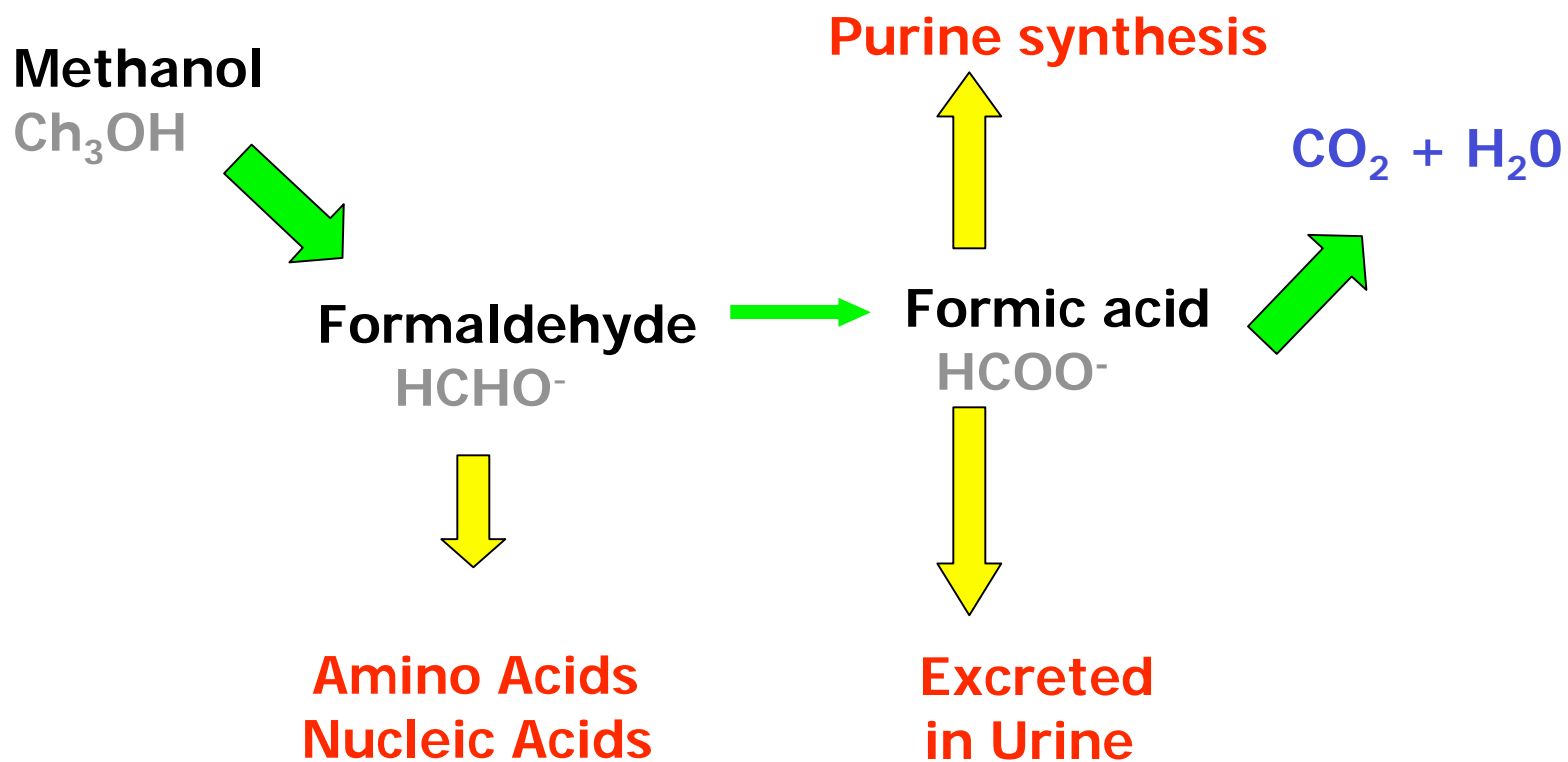


# Phenylalanine, Aspartic Acid & Methanol Content of Foods

	Phenylalanine*	Aspartic Acid*	Methanol
<b>12 oz diet beverage with aspartame</b>	<b>90</b>	<b>72</b>	<b>18</b>
12 oz milk	<b>606</b>	<b>888</b>	-
Medium banana	58	<b>146</b>	<b>21</b>
12 oz orange juice	36	<b>276</b>	<b>23</b>
12 oz tomato juice	58	<b>346</b>	<b>107</b>

\*amino acids\_

# Methanol Metabolism



# Methanol Metabolism

## Methanol



**Conversion very rapid:  
No accumulation**

**Accumulation of formic acid  
= toxicity of methanol**

**Normal range in blood  
= 7- 63 mg/L**

**Lowest blood level associated with toxicity = 126 mg/dL  
Safe dose = 2 gm for adult**

Kostic and Dart, 2003

## Formaldehyde Metabolism

- Constituent of many foods
- Produced during the endogenous demethylation of foods and drugs, such as caffeine
  - One cup of coffee produces 30 mg of formaldehyde
- Essential in one-carbon pool metabolism.
  - Formic acid is a substrate for nucleotide synthesis
- Calculated >50,000 mg formaldehyde is produced and metabolized daily in an adult human body
- Adult human liver will metabolize 22 mg formaldehyde *per minute* to formic acid and CO<sub>2</sub> and water

Clary and Sullivan, 1999

# Effect of Aspartame on Blood Methanol & Formic Acid

Subjects	Dose (mg/kg): N	Methanol and formic acid (mg/dL)
Health adults	34 mg/kg; n=12	methanol < LOD*
	100 mg/kg; n=6	methanol peak <b>1.27</b> , <LOD at 8 hr
	150 mg/kg; n=6	methanol peak <b>2.14</b> , <LOD at 24 hr
	200 mg/kg; n=6	methanol peak <b>2.58</b> , <LOD at 24 hr No change in blood formic acid
Healthy Infants	34 mg/kg; n=10	methanol < LOD
	50 mg/kg; n=6	methanol < LOD
	100 mg/kg; n=8	methanol peak = <b>1.02</b> at 90 min, then ~0.45 at 2.5 hr
Healthy adults	600 mg <i>per hr</i> for 8 hr	No change in blood methanol or formic acid levels

Lowest blood level ~ toxicity = 126.0 mg/dL

\*LOD= limit of detection, 0.35 mg/dL

Stegink *et al.*, 1981, 1983, 1989

## Safety Evaluations of Aspartame

- Acute toxicity
- Subacute toxicity
- Chronic bioassays
- Neurotoxicity
- Teratogenesis
- Reproductive toxicity
- Genotoxicity
- Immunotoxicity
- Cytotoxicity
- Bacterial studies
- Human clinical studies
  - Blood chemistry, body wt
  - Methanol, formaldehyde
  - Headaches
  - Behavior and cognitive function
  - Induction of seizures
- Epidemiological studies

## Long Term Animal Studies-Cancer

- 5 with rats, doses up to 5000 mg/kg/d
- 3 with mice, doses up to 4000 mg/kg/d
- 3 with transgenic high cancer risk mice at doses up to 7500 mg/kg/d
- 1 with hamsters, doses up to 12,000 mg/kg
- 1 with dogs, doses up to 4000 mg/kg/d
- 2 with rats to assess promotion of existing cancers

## Long Term Animal Studies-Cancer

- 14/15 animal studies had negative findings indicating no evidence of carcinogenic effect or cancer promoting effect of aspartame
- One study concluded that aspartame has carcinogenic potential (Ramazzini Foundation)
  - This panel agreed with findings of numerous food authorities that Ramazzini study:
    - Numerous methodological and interpretation errors
    - Provided “no credible evidence that aspartame is carcinogenic”
    - “Is no need to further review the safety of aspartame”
    - “No need to revise previously established ADI”

## Studies during Pregnancy and Development

- Effect of aspartame studied during reproduction, pregnancy, lactation and development in rats, mice, hamsters, rabbits and humans
- No effect at doses up to 4000 mg/kg/day in rodents and 1600 mg/kg/day in rabbits
- No change in breast milk composition in humans at doses up to 50 mg/kg
- Conclusion – no evidence of adverse effects

## Studies on Headaches

- Have been several, conflicting results with most showing no effect; however some small studies suggesting may be a susceptible subset
- There is no known mechanism
- Is difficult to study - no objective measure, power of suggestion and inconsistent results

## Neurotoxicity-Learning Behavior

- Animal studies
  - Up to 4% of diet (4000 mg/kg/d), no effect on neuronal function, learning or behavior despite changes in blood and brain amino acids levels
- Human studies
  - Normal children, hyperactive children, children with PKU, aggressive school boys, sugar-sensitive children, airline pilots
  - Healthy adults, adults with Parkinson's disease, depression
  - No effect of aspartame on learning or behavior in all but 1 study

## Neurotoxicity-Seizures

- Animals - No effect - doses up to 1000 mg/kg/d
  - Evaluated in a variety of animal models to induce convulsions and seizures  
(Pinto and Maher, 1988; Guiso *et al.*, 1988; Cane *et al.*, 1989; Tilson *et al.*, 1989; Helai *et al.*, 1996)
  - Genetically epilepsy-prone rats  
(Daily *et al.*, 1991)
- Human studies - No significant effect on seizures observed with doses of 34-50 mg/kg
  - Children diagnosed with petite mal seizures, individuals with epilepsy, self-reported aspartame-sensitive adults  
(Camfield *et al.*, 1992; Shaywitz *et al.*, 1994, Rowan *et al.*, 1995)

# Epidemiological Studies

Author	Type of study (N)	Consumption of Asp	Conclusions
Olney (1996)	US SEER brain tumor data from 9 locations	<b>Not measured</b>	<b>Incidence increased after aspartame on market</b>
Gurney (1997)	56 brain tumor cases 94 controls	Dietary recall - Personal interview	<b>No association</b>
Hardell (2001)	30 brain tumor cases 45 controls	Recall of low calorie soft drinks.	<b>No association</b>
Bunin (2005)	315 children - brain tumor, 315 controls	Food frequency completed by mothers of children	<b>No association</b> between consumption during pregnancy and risk
Lim (2006) from NCI	Prospective study <b>473,984 subjects, 5 yr</b> Hematopoietic cancers (n=2,106); Brain cancers (n=376)	Food frequency questionnaires	<b>No associations</b> between hematopoietic or brain cancers and aspartame consumption
Gallus (2007)	Case control study- various cancer types (n = 8976 cases, 7028 controls)	Food frequency questionnaires	<b>No association</b> between cancer and sweetener consumption

## Aspartame - Summary

- **Metabolism is well understood and follows that of other common foods.**
- **Consumption, even at levels much higher than that expected under typical circumstances, has virtually no impact on levels of blood constituents such as amino acids, methanol or glucose.**
- **A well-studied sweetener whose safety is clearly documented and well established through extensive laboratory testing, animal experiments, epidemiological studies and human clinical trials.**

## Aspartame

- **No credible link between consumption of aspartame at levels found in the human diet and conditions related to the nervous system and behavior, nor any other symptom or illness.**
- **Non-genotoxic and there is no credible evidence that aspartame is carcinogenic.**
- **Does not increase hunger in those who use it; to the contrary, studies indicate it might be an effective tool as part of an overall weight management program.**

## Panel Conclusions

- **Aspartame is a well-characterized, thoroughly studied, high-intensity sweetener that has a long history of safe use in the food supply and can help reduce the caloric content of a wide variety of foods.**

Critical Reviews in Toxicology, 37:629–727, 2007

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