Non-caloric sweeteners and special groups: children and pregnant women

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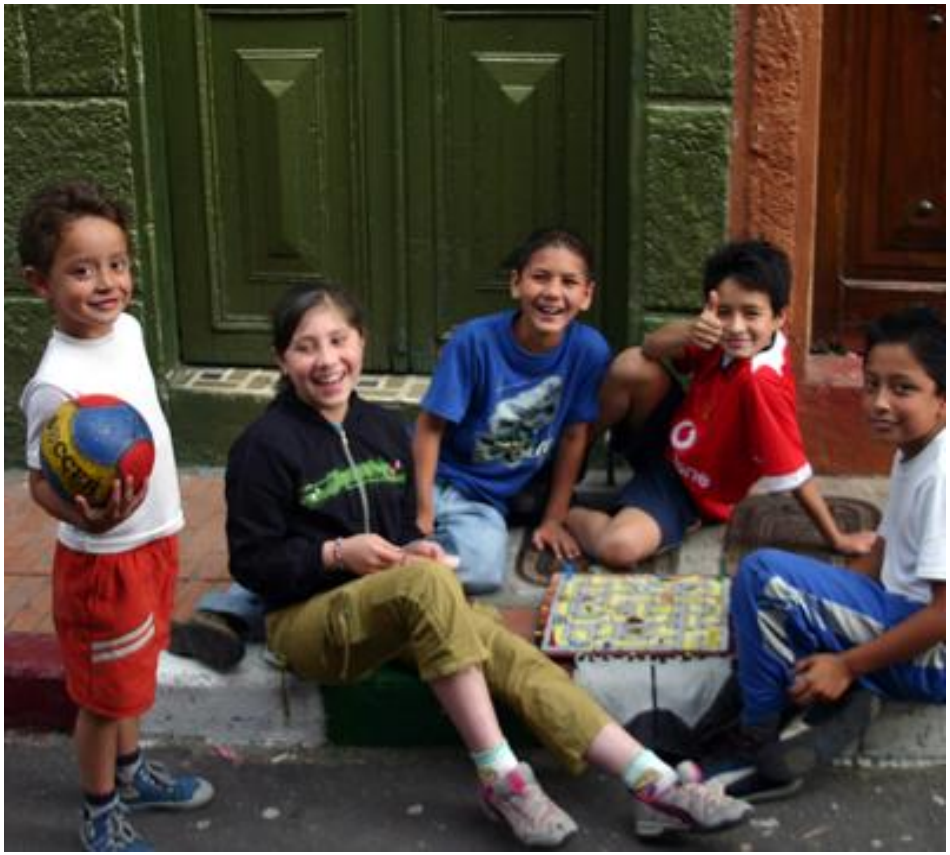
Introduction – why special?

- Time of rapid growth and development.
- Need calories and nutrients.
- Generally - recommend intake of nutrient-rich foods and beverages.

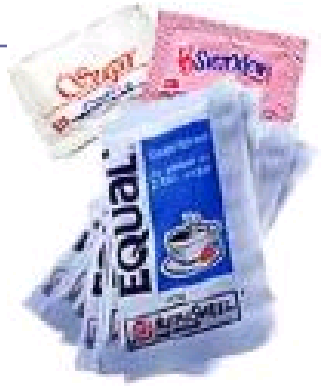
Introduction – why special?

- Consumption of non-caloric sweeteners useful to:
  - Control weight gain
  - Control blood sugar



Outline

- Introduction
- The controversies
- The data
- Children
- Pregnant women
- Conclusions



Controversy

- *“Aspartame breaks down into methanol and excitatory amino acids that affect the brain, so that is why aspartame is toxic.”*
- *TRUE OR FALSE??*

The answer -

- *"Aspartame breaks down into methanol and excitatory amino acids that affect the brain* - **TRUE – aspartame is completely digested in the intestine, and amino acids are used by body, including brain.**

…….so that is why aspartame is toxic."

FALSE! **– *levels of amino acids and methanol in aspartame are no higher than the amount found in common foods.***

Phenylalanine, Aspartic Acid & Methanol Content of Foods

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

*amino acids

All amounts in mg

Controversy

- *“Aspartame breaks down into methanol and methanol can cause methanol poisoning. Therefore aspartame is toxic because it causes methanol poisoning.”*
- *TRUE OR FALSE??*

The answer

- *"Aspartame breaks down into methanol –*
- **TRUE – aspartame contains a methyl group. As with many foods, methanol is released during digestion.**
- *" Methanol can cause methanol poisoning".*
- **TRUE – at HIGH levels which cause build-up in blood.**
- *"Therefore aspartame is toxic because it causes methanol poisoning."*
- **FALSE! – Amount of methanol in aspartame & other foods is too low to change blood levels.**

Methanol metabolism

Methanol

Alcohol dehydrogenase in liver

Formaldehyde
T½ = 1.5 min

Formic acid
T½ = 3-6 hr

Tetrahydrofolate intermediate

$CO_2 + H_2O$

Conversion very rapid
No accumulation

Accumulation of formic acid = toxicity of methanol

Lowest blood level of methanol ever associated with toxicity = 126 mg/dL

Kostic and Dart, 2003

Formaldehyde – sounds scary!

- is a constituent of many foods!
- produced during metabolism of foods and many drugs
  - Caffeine from 1 cup of coffee = 30 mg formaldehyde
- is essential in one-carbon pool metabolism.
  - Formic acid used in synthesis of nucleotides for DNA
- Is calculated that >50,000 mg formaldehyde is produced and metabolized daily in an adult human
- adult human liver can metabolize 22 mg formaldehyde *per* minute – so very rapid metabolism.
- Also rapid metabolism in young humans

Clary and Sullivan, 1999

Effect of aspartame on blood methanol and formic acid

Subjects	Dose (mg/kg)	Methanol and formic acid (mg/dL)
Health adults (intake from food/beverage Average= 5 High = 15 mg/kg	34 mg/kg 100 mg/kg 150 mg/kg 200 mg/kg	→ methanol – not detected (ND) → methanol peak level 1.27, ND at 8 hr → methanol peak level 2.14, ND at 24 hr → methanol peak level 2.58, ND at 24 hr No change in formic acid levels
Healthy Infants Stegink *et al*., 1981, 1983, 1989	34 mg/kg 50 mg/kg 100 mg/kg	→ methanol – not detected → methanol – not detected → methanol peak = 1.02 No change in formic acid levels

Aspartame DOES NOT cause methanol poisoning

Methanol toxicity > 126.0 mg/dL; and accumulation of formic acid

Controversy

- *"Aspartame causes neurological damage, including behavior problems, headaches/migraines, dizziness, seizures, epilepsy, nausea, numbness, muscle spasms, depression, fatigue, irritability, insomnia, vision problems, hearing loss, breathing difficulties, anxiety attacks, slurred speech, loss of taste, vertigo, and memory loss"*
- *TRUE OR FALSE??*

http://www.mercola.com/article/aspartame/dangers.htm

The answer

- *"Aspartame causes neurological damage, ….. and memory loss."*
- **FALSE - Many studies have been conducted and have found no effect, even at levels much higher than humans consume.**
  - Many accusations and individual reports - but an overwhelming number of research studies find no effect as discussed in next slides.

Learning and 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 (many studies). At 9% diet, impaired learning as have nutritional imbalance with high levels of 2 amino acids.
- Controlled Human studies
  - Normal children, hyperactive children, children with PKU, aggressive school boys, sugar-sensitive children (many references)
  - Healthy adults, airline pilots, adults with Parkinsons disease, adults with depression.
  - **No effect in all** except 1 study on depression – not replicated

Reviewed in Magnuson et al., 2007

Seizures?

- No effect on seizures - 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)
- No significant effect on seizures observed in controlled human studies 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)

Reviewed in Magnuson et al., 2007

Headaches?

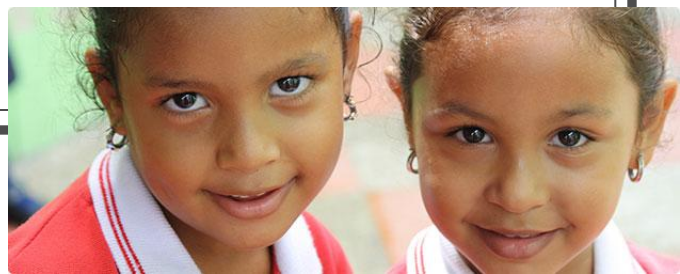
- Have been several, conflicting results with most showing no effect; however some small studies suggesting may be a susceptible subset.
- There is no known mechanism.
- Is a difficult endpoint to study as there is no objective measure for headache – must be self reported, susceptible to power of suggestion.

Reviewed in Magnuson et al., 2007

Is aspartame safe for children?

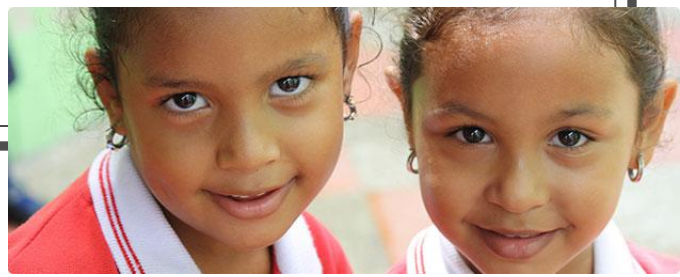
- Metabolism of aspartame
  - No difference between children and adult
- Effect on behavior extensively assessed
  - No effect even with habitual use
- Effect on childhood cancers
  - No association (Bruin *et al*. 2005)

Aspartame is safe for children (>1 yr) at levels currently consumed



Are steviol glycosides safe for children?

- Safety has been demonstrated for purified steviol glycosides and approval for purified preparations.
- Animal studies found no effects of purified steviol glycosides on development and growth.
- Few studies have been reported on steviol glycosides and children.



Are sweeteners safe for pregnant women?

- Aspartame –
  - Many animal studies conducted demonstrate no effect on reproduction, pregnancy outcome, development of offspring.
  - Two recent reports need to be addressed:
    - 1. Rat study by Soffritti *et al*., (2010)
    - 2. Cohort study by Halldorsson *et al.,* (2010)
  - EFSA reviewed and concluded these studies do not provide evidence that aspartame was causative factor.

(EFSA Journal 2011;9(2):2089)

Aspartame Administered in Feed, Beginning Prenatally ….. in Male Swiss Mice

- Pregnant mice were fed aspartame in ‘‘Corticella diet’’ at doses equivalent to 242, 987,1919 and 3909 mg/kg/day. Offspring then fed same diets as mothers.
- Main finding reported by authors – increase in liver and lung tumors in male offspring of rats fed highest doses.
- This group has published several studies on aspartame and each time, report increased cancer at different site/sex. Methodology and interpretation has been reviewed and criticized by many authorities, including EFSA.
- NOTE - 14 other animal studies and 6 epidemiological studies have found **no** evidence of increased cancer.

Soffritti *et al*. (2010)

"Artificially sweetened soft drinks and risk of preterm delivery"

Large study of 59,334 Danish pregnant women

- Reported higher odds ratio for risk of preterm delivery in women who consumed >4 servings/d
- Strengths – large study, diet information collected
- Limitations - Small number report >4 servings, also differences in BMI, smoking, social status, single – authors state was adjusted for.
  - propose effect due to methanol from aspartame
  - did not consider other dietary factors, or determine which sweetener was consumed.

Halldorsson *et al.* 2010

Are sweeteners safe for pregnant women?

- Stevia and Stevia glycosides
  - Crude extracts of Stevia plant are NOT recommended as adverse effects have been reported.
  - Studies on the highly purified steviol glycosides that are approved for use, have found no effects on reproduction and development.

Reproductive Toxicity Studies – Purified Steviol Glycosides

Reb A (97% purity) was administered via the diet to rats for two generations (Curry et al., 2008).

- No effect in either the F_0 or F_1 generation
  - body weight, body weight gain, food consumption.
  - reproductive performance: mating performance, fertility, gestation lengths, estrous cycles, or sperm motility, concentration, or morphology.
  - Survival, reflex development, body weight, sexual maturation
  - Highest dose ~ 2,000 mg/kg bw/day.

Conclusions

- Children and pregnant women are at higher risk for toxicity for all compounds because of increased consumption, rapid growth and development.
- This is understood when data is reviewed for regulatory approval and ADIs are established for sweeteners.

Conclusions

- Well-designed controlled studies support that aspartame and purified steviol glycoside sweeteners are safe for children and pregnant women at use levels currently consumed, which are well below the established ADIs.

Thank you!

Questions?

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