Addressing Questions about Aspartame and Stevia Sweeteners:
Facts Health Professionals Need to Know

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Outline

• Overview of safety evaluation process
• Aspartame –
  − Controversies and answers
• Stevia sweeteners
  − What are they?
  − What are the differences between extracts and purified preparations?
Premarket Safety Evaluation

- Before high intensity sweeteners are approved for use in foods and beverages, a comprehensive safety evaluation is conducted
- Safety = hazard X exposure
- Assess potential hazard in toxicology studies:
  - Acute, Sub-chronic, Long-term toxicity studies in multiple species
  - Carcinogenicity
  - Genetic toxicity
  - Reproductive toxicity
  - Teratogenicity
  - Also human studies – blood chemistry, special populations such as diabetics

Safety Evaluation

1. Identify Hazard
2. Characterize Dose-Response
3. Estimate Acceptable Daily Intake (ADI)

ADI Values

- Data reviewed by international food authorities (JECFA, FDA, Health Canada, EU, etc.) to establish ADI
- Acceptable Daily Intake (ADI) = amount considered safe to consume every day for a lifetime 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
Safety Evaluation

- Identify Hazard
- Characterize Dose-Response
- Assess Exposure
- Estimate Acceptable Daily Intake (ADI)
- Estimate Range/Distribution of Human Intakes
- Characterize Risk

Food survey for target population

Aspartame

- Discovered in 1965
- 200 X sweet as sucrose
- Approved in over 130 countries, approved food additive in Canada
- JECFA ADI: 40 mg/kg/day
- FDA ADI: 50 mg/kg/day

Consumption studies: Australia, Brazil, Canada, Denmark, France, Germany, Italy, Korea, Netherlands, New Zealand, Portugal, Spain, Sweden, UK, US.

Average users: <1-10% ADI; Highest users: 45% ADI

No report of even highest user exceeding ADI

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

Not Sweet

Breakdown products safety also evaluated
Controversy

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

Aspartame Absorption in the Gut

Intestinal Lumen Mucosa Cell Portal Blood

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

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

*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 is metabolized in the liver by alcohol dehydrogenase.
- The reaction yields formaldehyde and CO₂.

Conversion very rapid:

- No accumulation observed.
- T₁/₂ = 1.5 min

Methanol:
- Essential in one-carbon pool metabolism.
- Adult human liver will metabolize 22 mg formaldehyde.
- Lowest blood level associated with toxicity = 126 mg/dL
- Alcohol dehydrogenase in liver

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 CO₂ and water

Formaldehyde:
- Safe dose = 2 gm for adult
- No change in blood formic acid
- Normal range in blood = 7-63 mg/L

Effect of Aspartame on Blood Methanol & Formic Acid

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Dose (mg/kg): N</th>
<th>Methanol and formic acid (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy adults</td>
<td>34 mg/kg: n=12</td>
<td>methanol &lt; LOD*</td>
</tr>
<tr>
<td></td>
<td>100 mg/kg: n=6</td>
<td>methanol peak 1.27, &lt;LOD at 8 hr</td>
</tr>
<tr>
<td></td>
<td>150 mg/kg: n=6</td>
<td>methanol peak 2.14, &lt;LOD at 24 hr</td>
</tr>
<tr>
<td></td>
<td>200 mg/kg: n=6</td>
<td>methanol peak 2.88, &lt;LOD at 24 hr</td>
</tr>
<tr>
<td>Healthy Infants</td>
<td>34 mg/kg: n=10</td>
<td>methanol &lt; LOD</td>
</tr>
<tr>
<td></td>
<td>50 mg/kg: n=6</td>
<td>methanol &lt; LOD</td>
</tr>
<tr>
<td></td>
<td>100 mg/kg: n=8</td>
<td>methanol peak 1.02 at 90 min, then</td>
</tr>
<tr>
<td></td>
<td></td>
<td>=0.45 at 2.5 hr</td>
</tr>
<tr>
<td>Healthy adults</td>
<td>400 mg per hr for 8 hr</td>
<td>No change in blood methanol or formic acid levels</td>
</tr>
</tbody>
</table>

*LOD: limit of detection, 0.35 mg/dL.

Controversy

• “Aspartame causes cancer.”
• TRUE OR FALSE??

Genotoxicity and animal studies

• Genotoxicity studies in animals, cells and bacteria studies have shown aspartame does NOT cause mutations
• 16 chronic animal studies: multiple species
  – 14 found no evidence of carcinogenic or promoting effects of aspartame
  – Only studies reporting positive results are by Soffritti et al.
• Detailed review of protocol and data of Soffritti by numerous experts: EFSA; FDA; Health Canada; US National Toxicology Program; International expert panel (Crit Rev Toxicology, 2007)
• All conclude that:
  – Are serious flaws in methodology and interpretation in Soffritti study
  – “there is no credible evidence that aspartame is carcinogenic”
  – “no need to revise previously established ADI”

Epidemiological Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study (N)</th>
<th>Consumption of Aspartame</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olney</td>
<td>US SEER brain tumor data from 9 locations</td>
<td>Not measured</td>
<td>Incidence increased after aspartame on market</td>
</tr>
<tr>
<td>Gurney</td>
<td>36 brain tumor cases, 94 controls</td>
<td>Dietary recall - Personal interview</td>
<td>No association</td>
</tr>
<tr>
<td>Hardell</td>
<td>50 brain tumor cases, 45 controls</td>
<td>Recall of low calorie soft drinks</td>
<td>No association</td>
</tr>
<tr>
<td>Nurse</td>
<td>315 children - brain tumor, 315 controls</td>
<td>Food frequency completed by mothers of children</td>
<td>No association between consumption during pregnancy and risk</td>
</tr>
<tr>
<td>Lim</td>
<td>Prospective study 473,984 subjects, 5 yr Hematopoietic cancers and Brain cancers</td>
<td>Food frequency questionnaires</td>
<td>No associations between hematopoietic or brain cancers and aspartame consumption</td>
</tr>
<tr>
<td>Statkus</td>
<td>Case control; various cancers (976 cases, 728 controls)</td>
<td>Food frequency questionnaires</td>
<td>No association between cancer and sweetener</td>
</tr>
<tr>
<td>P.</td>
<td>Cancer control; various cancers (1019 cases, 2107 controls)</td>
<td>Food frequency questionnaires</td>
<td>No association between cancer and sweetener</td>
</tr>
</tbody>
</table>
The answer

- Preclinical studies
  - aspartame does NOT cause mutations in DNA
  - aspartame does NOT cause cancer in animals in most studies conducted
  - positive studies all conducted by one lab - serious flaws.
- Epidemiological studies
  - if measured consumption – all find no association

Aspartame consumption does not cause cancer.

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

Effect of aspartame on seizures?

- **No effect on induction or duration of 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 petit 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 consumption by 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

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

Stevia sweeteners

- Hot-water extracts from the leaves of the South American shrub Stevia rebaudiana.
- Extracts can then be further purified to meet specifications established by JECFA for commercial sweeteners allowed in foods and beverages.
Stevia sweeteners

- Sweetness is provided by various steviol glycosides, such as Rebaudioside A and stevioside.
- Are many different steviol glycosides

Metabolism

- Glucosides not absorbed or digested by small intestine
- Steviol glycosides hydrolysed to steviol by gut microflora
  - Rate depends on number of glucose moieties attached to steviol backbone
- Steviol absorbed in large intestine, glucuronidated and excreted
  - Rats: faeces
  - Humans: urine

Stevia sweeteners: Safety

Comprehensive battery of safety studies have been conducted and reviewed by JECFA and other food authorities -

- Studies conducted with crude or low-purity extracts reported some adverse effects on blood pressure, blood glucose, kidney function and reproduction.
- Studies conducted with high-purity extracts (>95% steviol glycosides) have shown no adverse effects.
Stevia sweeteners

- JECFA established specifications for sweeteners to be used in foods and beverages:
  - at least 95% purified steviol glycoside (such as Rebaudioside A or stevioside)
- JECFA ADI = 4 mg/kg/day, as steviol equivalents
- United States
  - Manufacturers producing stevia-based sweeteners meeting JECFA specifications notify FDA of determination of Generally Recognized as Safe (GRAS) – can use as general purpose non-nutritive sweetener.

Stevia sweeteners

- Are the newest sweeteners in the market
- Marketing often promotes "natural" origin
- Extracts that have not been purified to meet JECFA specifications are not approved for food used, but may be sold as dietary supplements or natural health products.
- Is confusing for consumers that the "most natural and unrefined" is not approved for commercial use due to adverse effects observed with unpurified extracts.

Conclusions

- Aspartame and purified stevia sweeteners have undergone extensive safety testing and international regulatory agency review.
- Their intense sweetness can be safely utilized by consumers to enjoy sweet taste with fewer calories and without raising blood sugar levels.
OBJECTIVES OF THIS SESSION:

- To understand the role of low- and no-calorie sweeteners in the prevention and treatment of nutrition-related conditions such as obesity and diabetes
- To advise consumers on the appropriate use of these sweeteners to reach goals for weight management and diabetes management

HOW DID WE GET HERE?

- Lifestyle changes are major causes for the increase in these health concerns
- Lifestyle changes include changes in food patterns around the world and decreases in physical activity, which are contributors to the obesity epidemic, its consequences and type 2 diabetes

**HOW DID WE GET HERE?**

- How did these major changes occur?
  - Urbanization
  - Changes in food access
  - Lower cost of some food items
  - Obesogenic environment (media, fast food restaurants)
  - No time for physical activity

- Obes Res 2003, 11:1325-1332

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**Figure 1**

Urbanization, economic growth, technological changes for work, leisure, and food processing, mass-media growth

- Slow mortality decline
- Accelerated the expectancy, shift to increased DR-NC; increased disability period
- Reduced body fatness, reduced DR-NC

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**Figure 2**

WHAES, CARREDA

- Median 15 kcal/day
- 95 Percentile 50 kcal/day

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Source: Journal of the American Dietetic Association 2009; 109:1848-1853

(DOI:10.1016/j.jada.2009.08.007) Copyright © 2009 American Dietetic Association Terms and Conditions
WHAT DO WE KNOW?

- Obesity is a predisposing factor for type 2 diabetes, dislipidemias, high blood pressure
- Preventing overweight and obesity in the population is a challenge
- Steps for prevention must be taken
- Several factors may attenuate the escalation of weight gain in the global population
Many people are concerned about aspartame and stevia side effects. My co-speaker has already clarified the facts. What is true is that low- and no-calorie sweeteners can help reduce consumption of excess calories in the present diet.

**CONTROVERSY:**
- Do low- and no-calorie sweeteners stimulate appetite when consumed in non-energy-yielding products?
- This is not observed when low- and no-calorie sweeteners are consumed with other energy sources.
- This must be clarified in the context of global increases in BMI.

*Am J Clin Nutr 2009; 89:1-14*

**WHAT ARE THE FACTS?**
- Our preference for sweetness may be an evolutionary survival mechanism, ensuring the acceptance of breast milk with its slightly sweet taste from the milk sugar lactose, the primary carbohydrate present in human milk.

*Proc Nut Soc 1998; 57:639-643*
WHAT ARE THE FACTS?

- Investigations into newborns’ taste response uniformly indicate that they respond even to dilute sweet taste and will consume more of a sweet–tasting sucrose solution when compared to water.
- In the weaning process, sweetness makes foods more appealing and is often used to make new foods more acceptable to children.

J Ped Gastr Nutr 2009; 48:525-30

WHAT ARE THE FACTS?

SWEETNESS IS IMPORTANT

- Critical changes in eating patterns such as increased consumption of caloric sweeteners, fats, animal sources of food and processed foods are related to increases in obesity prevalence and early onset type 2 diabetes.
- Moreover, increased consumption of these foods along with sugar-sweetened beverages are critical elements in the shift in diet.

Am J Clin Nut 2009; 89:1-14
WHAT CAN BE DONE:
- Low- and no-calorie sweeteners have the potential to moderate sugar and energy intake while maintaining diet palatability.
- No harmful effects have been scientifically demonstrated regarding the use of low- and no-calorie sweeteners.
- Sweeteners such as aspartame and stevia may help people who are overweight or have type 2 diabetes to reduce calories.

WHAT CAN BE DONE:
- Several countries support the use of low- and no-calorie sweeteners.
- Most advise moderate use to achieve a balance in calorie consumption since body weight is an expression of energy intake vs. energy expenditure.

WHAT CAN BE DONE:
- It is the position of American Dietetic Association that consumers can safely enjoy a range of nutritive and nonnutritive sweeteners when consumed in a diet that is guided by current federal nutrition recommendations, such as the Dietary Guidelines for Americans and the Dietary Reference Intakes, as well as individual health goals.
WHAT CAN BE DONE:

- Since 1994, the European Union (EU) has approved low- and no-calorie sweeteners and stated that their use as sugar replacements will be regulated and subject to review.
- Since then, EU has accepted the challenge of evaluating new research and updating the regulations.

WHAT CAN BE DONE:

- Other countries take the position of recommending low- and no-calorie sweeteners in the context of following a balanced diet and as a tool to reduce energy consumption to prevent excessive weight gain and its complications.
  - www.inn.gob.ve

CONCLUSIONS:

- Low- and no-calorie sweeteners can save calories to help prevent excess weight gain and promote weight loss and help ameliorate complications due to excess sugar consumption.
- Aspartame and stevia are safe for human consumption.
- No increase in appetite has been reported from the use of low- and no-calorie sweeteners.