# FDA Case Study: The Safety of High Intensity Sweeteners

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Mitchell Cheeseman, Ph.D.

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## Why a High Intensity Sweetener Case Study?

- Sweeteners are a bit different
- Replaces one or more distinct food ingredients
  - Sugar, corn syrup, etc…
  - Exposure can be directly related to consumption of these ingredients and is self limiting
- Can be a controversial issue to some
- Can be an important part of healthy eating for some
- Typically a full spectrum of toxicity data is available at the outset

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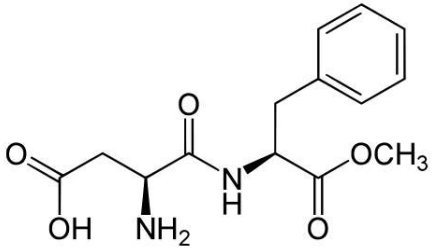
## Aspartame

- N-(L-α-Aspartyl)-L-phenylalanine, 1-methyl ester




- First authorized for use in the US July 1981 based on a safety review that had extended over 12 years

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## Aspartame Context

- First artificial sweetener to transit FDA's food additive review process before marketing
- Came to FDA in the wake of cyclamate issue
- Only saccharin on the market in the US

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# Aspartame 1981

- 200-times sweeter than sugar
- Metabolized to L-aspartic acid and L-phenylalanine
  - Amino acids naturally present in foods
  - Aspartame consumption does not impact consumer exposure to these amino acids
- Other impurities; diketopiperazine and methanol judged to be toxicologically insignificant
- FDA authorized limited uses initially

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## Component Amino Acids

- Aspartic acid in the diet
  - Oysters, avocado, asparagus, molasses, sugar beets, beef, pork and poultry
  - 100 grams of beef contains about 2400 mg of aspartic acid
  - Per capita U.S. intake of beef (59g/p/d) contains ~1400 mg
  - 23 mg/kg/d
- Phenylalanine in the diet
  - Soybeans, parmesan cheese, seeds, beef, chicken, turkey and pork
  - 150 grams of beef contains about 1500 mg of phenylalanine
  - Per capita U.S. intake of beef (59g/p/d) contains ~900 mg
  - 15 mg/kg/d

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# Aspartame 1981

- Early Exposure Estimates
  - FDA used multiple conservative approaches
  - Assume replacement of all sugar 8.3 mg/Kg-d
  - Assume replacement of all carbohydrates* 25 mg/Kg-d
  - Food survey data covering aspartame uses
    - Mean intake 2-5 years old 11.1 mg/Kg-d
    - 90$^{th}$ percentile 2-5 years old 25 mg/Kg-d
    - Mean intake adults 2.4 mg/Kg-d
    - 90$^{th}$ percentile intake adults 5.9 mg/Kg-d
    - **All values assumed broader uses than actually permitted**
  - FDA also used a higher level in discussion of the safety decision to emphasize the margin of safety 35 mg/Kg-d

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# Aspartame 1981

- FDA Determined the critical studies submitted included:
  - A 2-year feeding study in dogs
  - A 2-year feeding study in rats
  - A lifetime feeding study in in utero exposed rats
  - A long-term study in infant mice
  - Extensive clinical data on metabolism of aspartame and its component amino acids
- ADI determined to be 50 mg/Kg-d

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## Aspartame 1981-1993

- Carbonated beverages added 1983
  - Additional clinical data demonstrates no effects in humans at doses ranging from 30mg/Kg-d to 135 mg/Kg-d
  - ADI unchanged
  - EDI unchanged 25 mg/Kg-d
- Multivitamins added 1984
  - EDI increases < 1mg/Kg-d
  - ADI Unchanged

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## Aspartame 1981-1993 Cont'd

- New food intake survey data provided 1984-85
- Frozen confections teas and breath mints 1986
  - ADI, EDI unchanged
- Frozen desserts, cookies, yoghurt, milk-based drinks, gelatins and juices 1988
  - ADI unchanged; EDI 8.4mg/Kg-d
- Icings, glazes etc, candy, malt beverages, alcoholic beverages, baked goods and mixes 1993
  - ADI unchanged: 90$^{th}$ percentile EDI 17 mg/Kg-d

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## Aspartame 1996

- Permitted for use as a general sweetener
  - ADI unchanged
  - FDA revised the exposure estimate for all uses in food considering multiple approaches.
    - Using disappearance data
    - Using food consumption data
    - Assuming all sugars in the diet are replaced by aspartame

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## Aspartame 1996

- EDI based on food intake surveys
  - 0-23 months 21 mg/Kg-d
  - 2-5 years 25 mg/Kg-d
  - 6-12 years 18 mg/Kg-d
  - All Ages 12 mg/Kg-d
- EDI based on replacement of all sugars
  - Assumes added sugar intake of 1.56 g/Kg-d (93.6g/p/d)
  - Based on aspartame's sweetness and intakes of sweet food in surveys EDI =
    - Mean 8.7 mg/Kg-d
    - Pseudo 90$^{th}$ percentile all ages 22 mg/Kg-d (mean*2.5)
    - Pseudo 90$^{th}$ percentile 0-5 years 37 mg/Kg-d(all ages*1.7)

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## Aspartame 1996

- EDI based on disappearance data
  - Nutrasweet agreed to provide FDA with production and sales data for aspartame annually from 1982-1992
  - Per capita eaters-only intake 3.5 mg/Kg-d
  - All ages pseudo 90th percentile 8.8 mg/Kg-d
  - 0-5 years pseudo 90th percentile 15 mg/Kg-d

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## Aspartame More Recently

- FDA responded in 2011 to a citizen petition citing initial studies by the Rammazzini Foundation
- FDA had requested raw data on the animal studies published by RF as well as access to perform a GLP review of RF
- RF declined to offer FDA any data or the requested access. RF offered to sell data to FDA
- EFSA did receive limited data and cited significant issues with GLP compliance which call any results into question; EFSA confirmed safety in 2013
- NIH conducted a GLP audit which found similar problems

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## Aspartame Conclusions

- Although new uses were approved over time, the EDI FDA started with is essentially the same as the overly conservative estimate in 1981 25 mg/Kg-d
- This is due to improved data over time.
- Multiple methods of estimating exposure produce comparable results and, used together can create additional confidence in estimates
- Although substantial testing data continues to be developed, relevant data has not indicated a need to change the ADI
- Clinical data actually suggests a higher safe level

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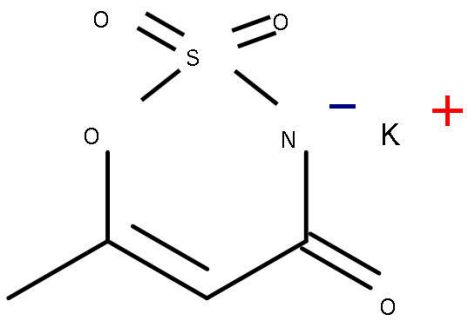
## Acesulfame Potassium

- Potassium 6-methyl-2,2-dioxo-2H-1,2λ6,3-oxathiazin-4-olate
- 200 times sweeter than sugar

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## Acesulfame Potassium

- Full range of toxicity studies submitted/ reviewed
- Review focused on 4 chronic studies and metabolism
  - 2-year study in dogs
  - Carcinogenicity study in mice
  - 2 chronic carcinogenicity studies in the rat with in utero exposure (one discounted)
  - Multiple metabolism studies (no evidence of any metabolism/uptake)

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## Acesulfame Potassium

- First approved in 1988 for limited uses
- ADI based on one long-term rat study is 15 mg/Kg-d
  - Not carcinogenic
  - Not mutagenic
  - No issues with reproductive development toxicity
- EDI for initial permitted uses is 1.6 mg/Kg-d
- EDI for current uses 4 mg/Kg-d

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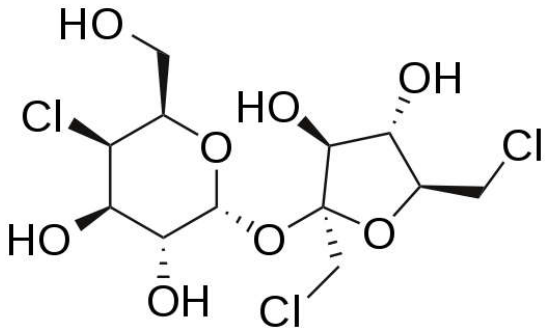
## Sucralose

- 1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside
- Between 320-1000 times sweeter than sugar

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## Sucralose

- First Approved for a wide variety of uses in 1998
- 90th percentile eaters only EDI 1.6 mg/Kg-d
- Full range of toxicity studies submitted
  - Not mutagenic
  - Not toxic to reproduction
  - Not teratogenic
  - Not neurotoxic
  - Not carcinogenic

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## Sucralose

- Only 20-30% uptake in humans
- Clinical studies to address diabetic consumption
  - No effects
- ADI based on carcinogenicity/ chronic study in the rat with the observed effect of weight gain decrement
- ADI = 5 mg/Kg-d

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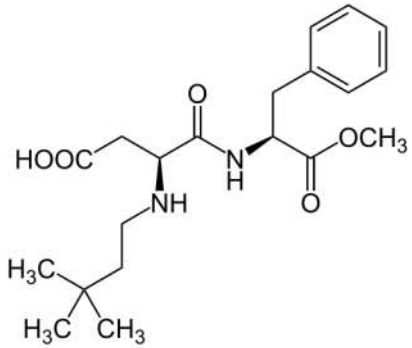
## Neotame

- (3S)-3-(3,3-Dimethylbutylamino)-4-[[(2S)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino]-4-oxobutanoic acid
- 7000-13000 times sweeter than sugar

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## Neotame

- First approved in 2002 for general use
- Highest 90th percentile eaters only EDI 0.17mg/Kg-d
- ADI 18-36 mg/Kg-d (Chronic dog rat and mouse; and reproduction (Rat))

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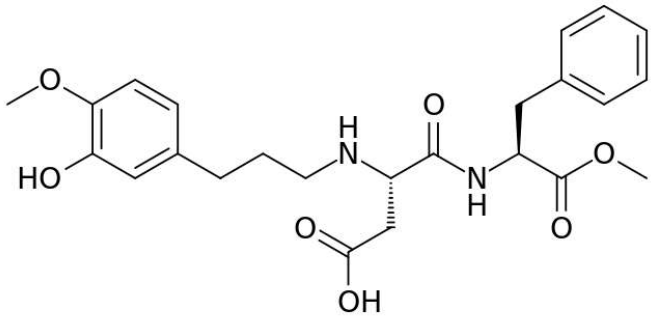
## Advantame

- (3S)-3-[3-(3-Hydroxy-4-methoxyphenyl)propylamino]-4-[[(2S)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino]-4-oxobutanoic acid
- 20,000 time sweeter than sugar

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## Advantame

- First approved in 2014 for general use
- Highest 90$^{th}$ percentile eaters only EDI 3.3 µg/Kg-d
- ADI based on the one-year chronic phase of a combined in utero chronic toxicity carcinogenicity study 32.8 mg/Kg-d

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## Final Thoughts

- Artificial sweeteners all have a substantial toxicity database supporting their use before they achieve significant penetration in the US market
- Use is self limiting and competing products will work to reduce individual exposure
- Initial exposures based on limited data can be protective long term
- Multiple (data sources/ approaches to estimations) can be combined to provide confidence in estimates
- Aspartame, acesulfame potassium (and sucralose) laid the groundwork for a modern systematic evaluation

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## Questions?

Mitchell Cheeseman
Managing Director
Steptoe, Washington
mcheeseman@steptoe.com



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