Public (Mis)Perceptions on Preservatives: A Case Study on Benzoates

Maia Jack, Ph.D., VP, Science & Regulatory Affairs

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AMERICAN BEVERAGE ASSOCIATION

Agenda

- IFIC 2017 Food & Health Survey
- CCFA Benzoate Background
- ICBA 2016 Benzoates Investigation – Exposure & Tox
- ADI Considerations
- Key Takeaways
- Appendix
  - How is safety of food additives established?
    - Risk characterization
    - Comparing NOAEL, ADI & EDI
  - ICBA Refined Benzoate EDI
  - Revisions to ADI – Interspecies Pharmacokinetics Variation

IFIC 2017 U.S. Food & Health Survey (foodinsight.org/FHS)

INTERNATIONAL FOOD INFORMATION COUNCIL FOUNDATION

Background

The International Food Information Council (IFIC) Foundation's *2017 Food & Health Survey*, "A Healthy Perspective: Understanding American Food Values," marks the 12th edition of an ongoing investigation into the beliefs and behaviors of Americans.

This year, the survey investigates important issues regarding consumer confusion, the food information landscape, health and diet, food components, food production, sustainability, and food safety.

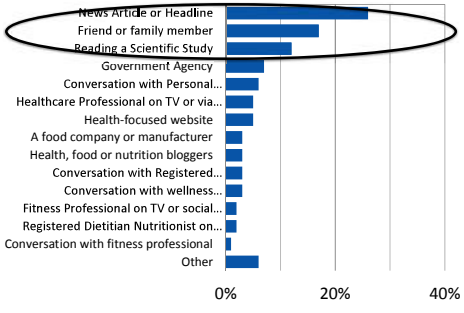
Methodology

- Online survey of 1,002 Americans ages 18 to 80. March 10 to March 29, 2017. Approx 22 minutes to complete.
- Significant trend changes from the 2016 results are noted with up and down arrows.
- The results were weighted to ensure that they are reflective of the American population ages 18 to 80, as seen in the 2016 Current Population Survey. Specifically, they were weighted by age, education, gender, race/ethnicity, and region.
- The survey was conducted by Greenwald & Associates, using ResearchNow's consumer panel.

News, family and friends influence safety concerns

These are top sources for all concerns, except GMOs (scientific study)

Top Source of Influence on Opinion about Top Safety Concern



Top Concern	#1 Source	#2 Source	#3 Source
Foodborne illness	News article or headline 36%	Friend or family 17%	Government agency 8%
Carcinogens	News article or headline 31%	Reading a scientific study 17%	Friend or family 13%
Chemicals in food	News article or headline 24%	Friend or family 20%	Reading a scientific study 10%
Pesticides	News article or headline 22%	Friend or family 18%	Reading a scientific study 11%
Food additives/ ingredients	Friend or family 21%	News article or headline 17%	Reading a scientific study 15%
Animal antibiotics	News article or headline 18%	Friend or family 18%	Reading a scientific study 13%
Biotech/GMOs	Reading a scientific study 25%	News article or headline 21%	Wellness counselor 11%
Allergens	Friend or family 24%	Personal health prof. 14%	Government agency 9%

Q: What one source of information most influenced your opinion on [your top safety concern]? (n=1,002)

2015 Study - Decision factors for purchasing food and beverages

If and how much do each of the following impact your purchases when you select foods and beverages at the grocery store?

Strong/Very Strong Impact on Purchase

1. Taste	**91.6%**
2. How fresh it is	88.2%
3. Is it a good value for the money	**84.9%**
4. Brand I trust	**75%**
5. Nutritional value	74.4%
6. What effects it could have on my health	70.8%
7. Are there chemicals in it	**63.7%**
8. How convenient it is: time saving/easy to prepare	55.6%
9. Where it originated - local, U.S., or country of origin (imported)	52.9%
10. Are there additives in it	**51%**
11. Are there preservatives in it	**49.4%**
12. How food is produced (conventional, organic, cage free, free range, etc.)	48.6%
13. What kind of packaging is it in	33.6%

Mothers with **low-to-moderate health literacy** "distrust of chemicals appears to stem from uncertainty concerning the potential consequences of exposure to chemicals from diet, or from a lack of understanding about chemicals in general."

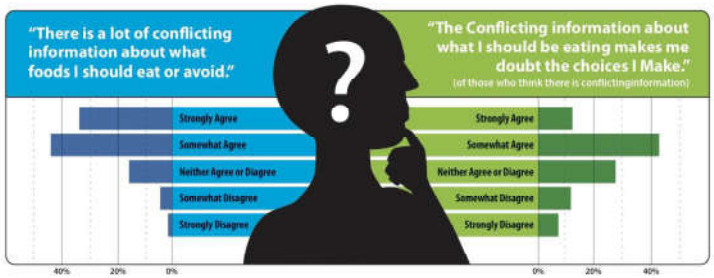
Whereas mothers with **proficient health literacy** more readily recognized that foods with some chemicals could provide benefits, such as longer shelf life, added vitamins, increased nutritional value, improved taste, decreased cost, aesthetics, decreased risk of "spoilage," and more pleasant aroma... man-made additives are not all inherently detrimental, and conversely could offer important health benefits.

Petrun, E.L., A. Flood, T.L. Sellnow, M.-S. Edge, K. Burns. 2015. Shaping Health Perceptions: Communicating Effectively about Chemicals in Food. Food Protection Trends, Vol 35, No. 1, p.24–35

Conflicting Advice Abounds

8 in 10 find conflicting advice about what to eat or avoid, many doubt their food choices

56% Of those who say there is a lot of conflicting information about what foods to eat/avoid say carcinogens is a top 3 issue, vs. **45%** of those who do not see conflicting info



Q: Do you agree or disagree with the following statements?
"There is a lot of conflicting information about what foods I should eat or avoid." (n=1,002)
"The conflicting information about what I should be eating makes me doubt the choices I make." (Of those who agree about conflicting information, n=775)

Jun 9, 2017 IFIC's Monthly Member Update "When is Too Much Not Enough?"

"… [W]e are gorging ourselves on food information, but **we're starving for nutritional literacy**."

"In a media environment where **sound science takes a back seat to slick headlines**, … without reliable information about food, **public health challenges** such as obesity, food safety, and chronic diseases will be **much more difficult to overcome**."

- Joseph Clayton, CEO

CCFA Benzoate Background

Benzoate Technological Justification

- Propensity for microbial spoilage in beverages not well understood or appreciated
  - GHP, HACCP and GMP - ALWAYS
  - Ubiquitous microflora - 100% sterile environment impossible
  - ALL tools needed to minimize risk of spoilage in beverages
- Product-to-product differences determine *whether*, *which* and *at what levels* preservatives are necessary
  - Beverage formulations, packaging, processing, storage and distribution conditions and inherent microflora
- Micro-challenge tests to assure functionality
  - Levels < Minimum Inhibitory Concentrations (MIC) can cause adaptation, acquired resistance and tolerance
- Example: strawberry flavor concentrate (not poor hygiene) origin of *Asaia Lannensis* acetic acid bacteria in spoiled strawberry-flavored beverage in spite of presence of 200 mg/kg benzoate
  - Kregiel, D., A. Rygala, Z. Libudzisz, P. Walczak, E. Oltuszak-Walczak. *Asaia lannensis – the spoilage acetic acid bacteria isolated from strawberry-flavored bottled water in **Poland***. Food Control 26 (2012): 147-150.
- No good substitutes for benzoates
  - Sorbates less effective, generate off-notes and present operational impediments (fountain systems)

2015 JECFA Assessment Triggered Safety Concern

- Estimated daily intake (EDI) among toddlers and young children at presumed 95th percentile consumer-only population exceeded Acceptable Daily Intake (ADI).
- Opportunities exist to refine assumptions both on exposure and hazard

International Council of Beverages Associations (ICBA) 2016 Benzoates Investigation Exposure & Tox

Refined Benzoate Estimated Daily Intake (EDI)

- Study Design
  - Countries included with ML > 250 mg/kg
    - Brazil, Canada, Mexico and U.S.A.
  - Designed to capture high intake populations
- Modelling Approaches
  - Individual-based data reflective of individual consumption patterns
    - Allows population breakdown by 'general population (per capita)'; 'consumers-only'; mean & 95th percentile; 'age breakouts;
    - Probabilistic modelling (chance of use level selected was based on market volume share)
    - Brand-loyal consumer modelling (worst-case scenario – max. level to main contributing category (i.e., regular CSD), market-weighted average to all others)
  - Probabilistic models and non-brand loyal categories – data based on market volume share.

Martin, D., A. Lau and A. Roberts. 2017. Benzoates intakes from non-alcoholic beverages in Brazil, Canada, Mexico and the United States. Food Additives and Contaminants. *Manuscript accepted.*

Refined Benzoate Estimated Daily Intake (EDI)

- 2016 ICBA exposure assessment approach meets and exceeds WHO Principles (EHC 240)
  - Individual dietary survey data (most precise)
  - Representative use levels based on market presence
  - Brand loyal 95th percentile consumer 'worst-case' scenario considered (not standard 90th percentile)
  - Individual foods approach – beverages (primary contributor to dietary benzoates)
  - Accurate model – specific uses for specific beverage types
  - Selected representative national markets to ensure adequate global protection
  - No chronic exceedance of ADI, even for worst-case scenario

Refined Benzoate Estimated Daily Intake (EDI)

- EDI from beverages - "No Safety Concern"
  - Based on 'high intake' markets
  - Refined complex exposure assessment model, using primarily individual dietary survey data
    - Market volume weighted use level information – representative of realistic consumer practices
  - Findings:
    - Toddlers/Children regular CSD brand loyal 95th percentile scenario results at ADI
    - Over a lifetime, EDI is below ADI – supports benzoate's long-term safe use
- Please see Appendix

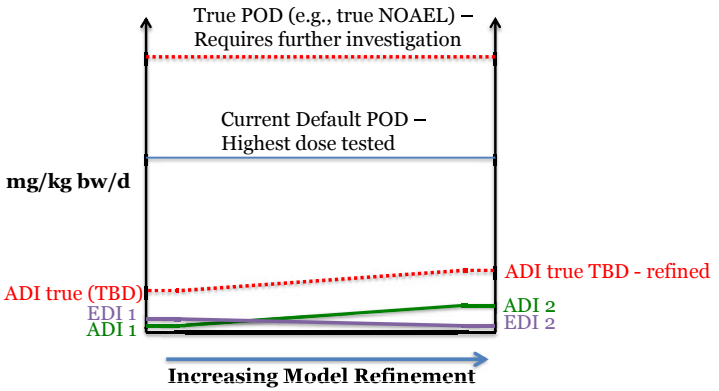
ADI Considerations

ADI Considerations

- JECFA ADI for Benzoates as Benzoic Acid
  - 0-5 mg/kg bw/day
  - Utilized 100X factor from Highest Dose Tested
  - The "default" **N**o **O**bserved **A**dverse **E**ffect **L**evel (NOAEL) – the highest dose tested – in pivotal study used for ADI
- Current JECFA ADI Conservative
  - Not based on a "true" NOAEL – could have been higher!
  - 100X Factor Conservative
    - Benzoic Acid metabolized and excreted similarly in rodents and humans – little interspecies pharmacokinetic variation suggests opportunity to reduce uncertainty factor by at least 4x
    - Opportunity to increase ADI by reducing 100X factor to 25X

Hoffman, T.E., and W.H. Hanneman. 2017. Physiologically-Based Pharmacokinetic Analysis of Benzoates in Rats, Guinea Pigs and Humans: Implications for Estimating Interspecies Uncertainty Factors in Risk Assessments. *Computational Toxicology* In press. (https://doi.org/10.1016/j.comtox.2017.06.002)

Benzoate Risk Characterization - Model Refinement



Next Steps

- ICBA/ABA Goal - Update benzoate safety point of departure (PoD) to derive an appropriate ADI
  - Develop a 2018 benzoate tox research plan
  - Conduct projects over the next few years.

Key Takeaways

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Key Takeaways

- Regional differences should not preclude support for science-based positions in Codex
- ICBA updated and refined benzoate exposure assessment for beverages
  - 'High intake' markets set the ceiling of exposures
  - Application of WHO criteria, including representativeness
- Results from this new assessment show **benzoates in beverages pose no safety concern** based on:
  - Chronically, EDI is below ADI – supports long-term benzoate's safe use;
  - Toddlers/Children reg CSD brand loyal 95th percentile scenario at ADI;
  - ADI based on default NOAEL (**not true NOAEL**), could be higher.
- Additionally, the uncertainty factor for interspecies pharmacokinetic variability can be reduced by at least 4-fold (increasing the ADI 4x from 5 to 20 mg/kg bw/d)

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Key Takeaways

- Reducing benzoates further, below 250 mg/kg (as benzoic acid) may result in:
  - Increased spoilage/food waste;
  - Reduction in product shelf-life;
  - Disproportionate impact on smaller manufacturers.
- Further reductions below 250 mg/kg are not scientifically warranted – adequate safety afforded

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Key Takeaways

Consumers deserve accurate ingredient safety information.

We must:

- Provide clear context around ingredient safety in view of propensity for media sensationalism
  - Communicate and contextualize ingredient safety properly to reassure consumers
- Manage uncertainty appropriately:
  - With generally accepted toxicological principles
  - And using **reasonable** assumptions

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Thank You

Maia Jack, Ph.D., VP, Science & Regulatory Affairs
American Beverage Association
mjack@ameribev.org
202-463-6756

Appendix

How is safety of food additives established?

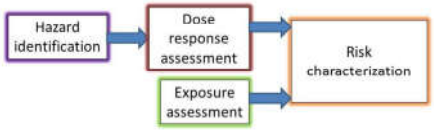
Risk characterization

Fundamentals of Food Additive Safety

- Dose makes the poison (Paracelsus)

Significant Electrolyte Imbalance = Death

- How to establish additive safety?



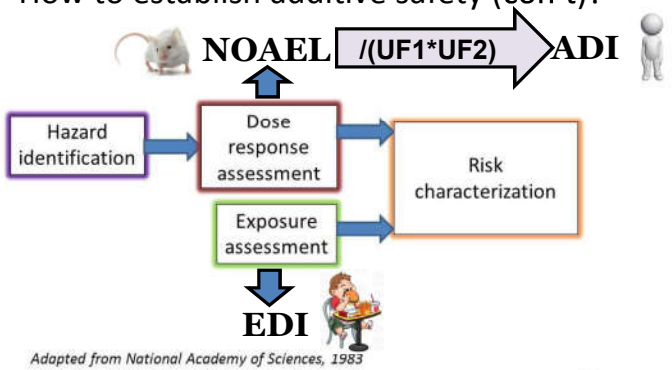
Adapted from National Academy of Sciences, 1983

Risk characterization

- How to establish additive safety (con't)?
  - Toxicology in rodents as surrogate for humans
  - Point of Departure (POD) may be No Observed Adverse Effect Level (NOAEL)
    - Incorporate precaution to extrapolate findings from rodents to humans - uncertainty factor UF1, traditionally 10x, lowered based on evidence
    - Incorporate precaution to account for human variability - uncertainty factor UF2, traditionally 10x, lowered based on evidence
  - Health-based guidance value is Acceptable Daily Intake (ADI) = NOAEL/(UF1xUF2)
  - Estimate risk by comparing the estimated daily intake (EDI) to ADI

Risk characterization

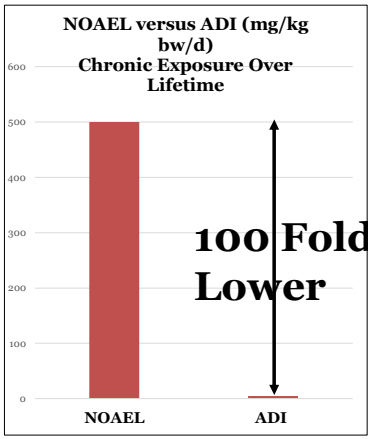
- How to establish additive safety (con't)?



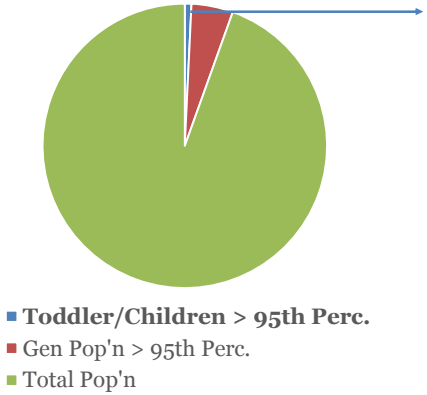
- Risk characterization: EDI v. ADI

Comparing NOAEL, ADI & EDI

- NOAEL (*over lifetime*)
- Traditional ADI = NOAEL/100 (UFs)
- Opportunity exists to lower UF to derive ADI based on evidence
- EDI = Daily food consumption pattern x Additive Use Levels in Foods (per person)



Estimated Daily Intake (EDI)

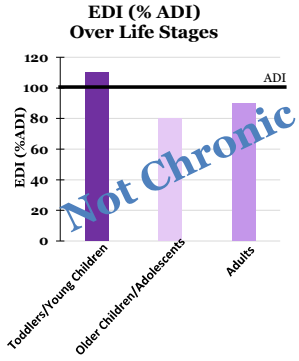


This sliver of the population (extreme outliers) - 95th percentile toddler/young children consumers - is being compared to ADI.

Comparing NOAEL, ADI & EDI

How to interpret EDI against ADI?

- EDI ≤ ADI
  - No further exposure refinement necessary
- EDI > ADI
  - Specific subpop?
  - Further refinement needed to seek more realistic scenarios
  - Verify exceedance across ALL life-stages
  - *Is ADI exceedance chronic across ALL life-stages?* No! Stop. No safety concern.



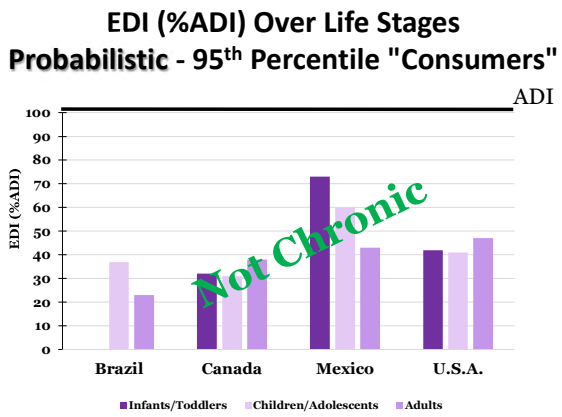
KEEP IN MIND –

ADI incorporates default 100x uncertainty factor from no observed adverse effect level in test species.

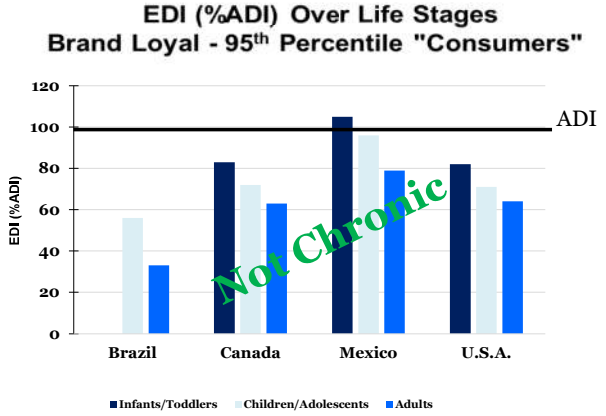
ICBA Refined Benzoate EDI

WHO EHC 240	ICBA 2016 Approach	80th JECFA	EFSA 2016
Individual dietary survey data - most precise	Individual dietary records	Primarily population-based Summary Statistics - CIFOCOOss	Population-Based Summary statistics
Additive concentration only for proportion of market used in, not whole food category	• "Representativeness" • Market volume weighted use level information • Applied to specific beverage types within 14.1.4.	Maximum of typical range (i.e., 209 mg/L) applied to entire 14.1.4 beverage category (no market representativeness)	No market representativeness Maximum levels from very specific foods applied to broader category (Examples for children/adolescents: • Crangon 3,800 ppm to 9.2. processed fish/fish products category; • Level of 150 ppm applied to entire 14.1.4. flavoured drinks category; Example for infants/toddlers: • Non-heat treated dairy-based desserts 117 ppm to entire 1.4. flavoured fermented milk products category when mean only 5 ppm!)
Brand loyalty	Brand-loyal 95th percentile consumer to regCSD at all pHs	-	Brand-loyal consumers to multiple food categories – overly conservative
Chronic dietary exposure, 90th percentile "consumers only" often represents high consumers	• Per capita/"consumers only" • Age subgroups • 95th percentile • All beverages • Major contributing beverage (i.e., Reg CSD)	• Per capita/ "consumers only" • Age subgroups • 95th percentile • All beverages (NOTE: 10.9 mg/kg bw/d upper bound in young children 1-7 yrs was established for "consumers only" based on 97.5th percentile of South Africa consumption data)	• Per capita/ "consumers only" • Age subgroups • 95th percentile • All foods, multiple major contributors
Dietary exposure to additive predominantly influenced by one food, use selected individual foods approach	Focus on water-based flavored drink category	Focus on: • beverages (reported use levels), • or, all foods (analytical)	All foods
Model accuracy - food consumption data and food chemical concentration data applied to same specific food;	NHANES coupled with market-weighted levels for same specific beverage type in 14.1.4. Accurate model	Not specific Broadly applied benzoate maximum typical use level (i.e., 209 mg/L) to entire 14.1.4. beverage category (NOTE: Unclear whether water was included under 14.1 relative to consumption amounts)	Not specific Broadly applied benzoate regulatory maximum limit (i.e., 150 mg/L) to entire 14.1.4. beverage category (See examples above) Outdated analytical data
Representative national populations to understand international situation	Representative national markets Brazil, Canada, Mexico, U.S.A. "worst-case" scenario markets – adequate global protection	CIFOCOOss primarily EUMS and China, Japan and Philippines (for relevant age breakouts)	EUMS
Chronic exceedance over life	No	No	No

Refined Benzoate EDI



Refined Benzoate EDI



Revisions to ADI – Interspecies Pharmacokinetics Variation

Endpoint	Human	Rat
Rate/Extent of Absorption	• Approximately 100% absorption after oral ingestion (e.g., Informatics, Inc., 1972 216-5980; IOMC, 2000 216-4218)	• Approximately 100% absorption after oral ingestion (e.g., Informatics, Inc., 1972 216-5980; IOMC, 2000 216-4218)
Rate/Extent of Metabolism	• Rapidly and completely metabolized (Informatics, Inc., 1972 216-5980; IOMC, 2000 216-4218; Tremblay and Qureshi, 1993 216-5939) • Peak plasma benzoic acid levels at 1-2 hours after oral administration (Kubota et al., 1988 216-5932; Kubota and Ishizaki, 1991 216-5930)	• Rapidly and completely metabolized (IOMC, 2000 216-4218; Bridges et al., 1970 216-5986; Thabrew et al., 1980 216-5984) • Peak plasma benzoic acid levels 3 hours after oral gavage administration (Adams et al., 2005 216-5922; JECFA, 1996 216-4405)[a]
Metabolites and Metabolic Enzymes	• Hippuric acid is the primary metabolite (Informatics, Inc., 1972 216-5980; IOMC, 2000 216-4218; Tremblay and Qureshi, 1993 216-5939) • At high doses (>500 mg/kg), benzoyl glucuronide is a secondary metabolite (Kubota and Ishizaki, 1991 216-5930; JECFA, 1996 216-4405) • Metabolism driven by conjugation with glycine; saturable process at high doses (i.e., ≥160 mg/kg) (Kubota et al., 1988 216-5932; Kubota and Ishizaki, 1991 216-5930; MacArthur et al., 2004 216-4214)	• Hippuric acid is the primary metabolite (Bridges et al., 1970 216-5986; Thabrew et al., 1980 216-5984) • At high doses (>500 mg/kg),[b] benzoyl glucuronide is a secondary metabolite (Adams et al., 2005 216-5922; JECFA, 1996 216-4405) • Metabolism driven by conjugation with glycine; saturable process at high doses (i.e., >120 mg/kg) (Schwab et al., 2001 216-5938; Gregus et al., 1992 216-7049; Simkin and White, 1957 216-6010; JECFA, 1996 216-4405)
Rate/Extent of Elimination/ Clearance	• 75-100% excreted as hippuric acid within 6-24 hours (Kubota et al., 1988 216-5932; Kubota and Ishizaki, 1991 216-5930)	• 75-100% excreted as hippuric acid within 24 hours (Bridges et al., 1970 216-5986; Thabrew et al., 1980 216-5984)

Zu, K., D.M. Pizzurro, J.E. Goodman, and T.A. Lewandowski. Consideration of Pharmacokinetic and Clinical Data in Deriving an Acceptable Daily Intake (ADI) for Benzoic Acid and Its Salts. Manuscript submitted.