Appendix I – Technological Justification for Benzoates

Executive Summary

Adoption of an adequate benzoate levels is critically important for beverage formulations that allow for product innovation, consumer choice and fair market competition while minimizing market disruptions. Important factors include:

- Intrinsic, extrinsic and process-related factors affecting susceptibility of water-based flavored drinks to microbial growth (examples are provided in the Detailed Comments below);
- The multi-hurdle multi-component preservative systems – including sanitation – employed by manufactures, where preservatives are only used at the lowest possible levels necessary to maintain product integrity;
- The potential for unintended consequences when using levels of benzoates at concentrations that are sub-lethal to the targeted microorganism (e.g., adaptation);
- The potential for inferior substitution in view of the superior performance afforded by benzoates:
    - Benzoates often are effective against organisms that are otherwise somewhat tolerant to sorbate and *vice versa*. Sorbates cannot be used in place of benzoates. However, in some formulations, sorbates and benzoates may be used in concert;
    - Sorbates are less effective as antimicrobials. Sorbates' degradation during the product shelf life may generate off-notes. Sorbates' lower solubility is likewise a challenge during beverage production and may cause operational impediments in fountain systems due to clogging of lines;
- Data on Minimum Inhibitory Concentration (MIC) of benzoic acid for common beverage spoilage microorganisms demonstrate that protective levels – which vary with pH and nutrient content – are at a minimum around 250 ppm for beverages with lower pH. Benzoic acid anti-microbial activity is pH-dependent. To be an effective anti-microbial, increased levels are needed for beverages with higher pH to ensure presence of adequate levels of undissociated form.
- Impacts on smaller beverage manufacturers.

As pH increases, the active undissociated form of benzoates in beverages decreases resulting in higher MIC in order to have the same functionality. A beverage with pH 4.3 and 500 ppm of benzoic acid has approximately the same amount of undissociated benzoic acid (active form) as a beverage at pH 3.5 with 250 ppm of benzoic acid. To compensate for losses in the active form of benzoic acid at higher pH, an exception is needed for these beverages.

Concentrates have different requirements than ready-to-drink (RTD) beverages. Concentrates are used in fountain systems and, due to the nature of the fountain business and the need for extended preservation post-mix, a bag of concentrate – not typically kept under refrigeration – may likely not all be consumed in a single day, depending on the number of customers visiting the Quick Service Restaurant. In comparison, RTD beverages are usually consumed in a single occasion. If the RTD beverage is not consumed in a single occasion, the container is usually sealed

and stored under refrigeration. The challenges associated with sorbate use are even more pronounced in concentrates. Sorbates' lower solubility causes clogging in fountain systems. Thus, higher levels of benzoates are required to guarantee adequate operation of fountain systems and microbiological stability of concentrates.

Detailed Comments

In commercial practice, water-based flavored drinks can be made unappealing or unpalatable by the growth of various fungi and acid tolerant bacteria resulting in the condition commonly referred to as "spoiled".[1]/ Microbiological activity can occur in "still" and "sparkling" (carbonated) beverages. Similarly, fountain syrups and some concentrates must also be preserved. In order to prevent undesirable microbiologically induced changes, manufacturers rely on sophisticated preservation systems – which consider the appropriate use of antimicrobials such as benzoic acid or its salts (benzoates).[2]/[3]/[4]/[5]/

The use of benzoates and other preservatives minimizes economic loss for the consumer and enhances convenience due to the reduced likelihood that the products will deteriorate and be discarded. Additionally, beverages can be offered at more affordable prices due to the cost-effectiveness of benzoates.

Benzoic acid occurs naturally in a number of foods including cranberries, prunes, cinnamon, cloves, green gage plums, huckleberries, raspberries, currants and others.[6]/[7]/ The keeping quality of these foods and their juices is in part attributed to their benzoic acid content.[7]/[8]/

Likewise, many water-based flavored drinks use benzoic acid or its various salts (commonly referred to as benzoates) as part of a total preservation system. Benzoates are most effective as preservatives in products with lower pH. Since the pH of water-based flavored drinks generally range from2.5 to 4.6, benzoates are a particularly useful tool to assure quality of these products.[9]/

Importantly, not all water-based flavored drinks contain benzoates. The need for benzoates is determined by beverage matrix, processing, packaging and storage conditions and the ubiquitous microflora of the environment, containers and ingredients. When used, benzoates maintain the quality, stability and integrity of beverages as part of a multi-component multi-hurdle preservative system.

Beverage susceptibility

Ensuring the safety and stability of today's increasingly complex global ready-to-drink (RTD) beverage landscape is paramount for manufacturers and microbiologists alike.[10]/ Research and development (R&D) cross-functional teams optimize formulations over a period of months to years considering safety, sensory attributes and manufacturability.

Beverages support microorganism growth due to a multitude of factors. Intrinsic, extrinsic and process-related factors must all be considered when selecting the optimal preservative system.[11]/[12]/ Intrinsic factors influencing microorganism growth in beverages are formulation-specific and may include pH, degree of carbonation, juice content and preservative systems.

Although beverage pH determines the availability of benzoic acid active form, concentrations required to avoid spoilage are particularly sensitive to beverage formulations as well. Extrinsic factors may include climatic and transportation conditions, temperature and duration of food storage, and packaging characteristics. Process-related factors may include changes in food composition and in microbial populations that result from processing (e.g., thermal processing such as pasteurization and resultant shifts from mixed microbial populations to populations of heat-resistant microorganisms [thermophilic spore formers, thermoduric organisms, etc.]).

Cold-filled beverages, especially those stored in the absence of refrigeration, may require an effective ingredient preservative. Use of an effective ingredient preservative may be necessary even in cold-filled beverages without juice. "Cold-filled" describes a bottling process in which the beverage is packaged into a container at ambient temperatures (or less) to preserve the integrity of ingredients prone to heat-induced degradation (e.g., extracts). Cold-fill packaging is commonly used for carbonated soft drinks and still beverages.

Concentrates may also require effective preservative ingredients. Concentrate bags are used in fountain systems and, after opened, may not be consumed in one single day. Additionally, the bags are not kept under refrigeration. Clearly concentrates are even more susceptible to microbiological spoilage than ready to drink beverages due to longer and more intense exposure to the environment. Therefore, additional protection against spoilage microorganisms may be necessary.

In all cases and scenarios, the global beverage industry follows current Good Manufacturing Practices (cGMPs) and only uses preservatives at the lowest levels necessary to maintain product integrity.

Role of sanitation in processing

Preservatives are not substitutes for proper sanitation. The successful deployment of preservatives is very much dependent on rigorous sanitation and cGMP-compliance.[13]/ Proper sanitation should ensure any initial bio-burden in beverages is exceedingly low. Sound sanitation and cGMP-compliance are critical components of the multi-hurdle preservative system.

However, despite rigorous implementation of the best sanitation standards, hazard analysis and control of critical points, it is not uncommon for a low numbers of microorganisms to be carried into the beverage. This may happen due to absence of complete sterile ingredients (e.g., water, syrup, juice) and environments (e.g., air, contact surfaces). A single microorganism entering a beverage can result in spoilage in the absence of effective preservative agents. Thus, antimicrobial preservatives are an important component of the multi-hurdle preservative system. Targeted concentrations of antimicrobial preservatives should always be greater than the Minimum Inhibitory Concentration (MIC). An equivalent or lower concentration enables adaptive behavior among spoilage organisms that can result in the onset of permanent tolerance.[14]/[15]/[16]/[17]/[18]/[19]/[20]/[21]/

Adaptation and Evolution

"Adaptive mechanism" is broadly understood as an evolutionary process in which organisms "adapt" to possible stressors in a particular environment. Various spoilage organisms may exhibit an "adaptive response" to both benzoic acid and sorbic acid in which successively transferred cultures are able to grow in the presence of successively higher concentrations of the weak acid preservatives.

The presence of preservatives (or disinfectants/antimicrobials) at sub-lethal concentrations may have the unintended consequence of "adaptation" via selection of microorganisms with a series of permanently fixed mutations leading to permanent evolutionary events.[14-21]/ Naturally derived tolerance to sorbic acid through the presence of genes causing degradation of sorbic acid to 1,3-pentadiene has long been a reason to employ benzoic acid in combination with sorbic acid.[22]/[23]/ Therefore, before committing to extreme reductions in maximum levels of preservatives in beverages, microbiological and genetic studies at sub-lethal concentrations are warranted and should be conducted.

Role of benzoic acid and its salts in beverages

Benzoates have a long history of safe use in foods. They are the preservatives of choice for soft drink manufacturers due to their low toxicity, effectiveness against common beverage spoilage microorganisms, stability, good solubility, lack of color and mild flavor.[2]/[3]/ As early as 1909, the "harmlessness" of sodium benzoate as a food preservative was extensively verified in actual human feeding studies performed by three independent research organizations under the direction of the U.S. Secretary of Agriculture.[24]/

Benzoic acid is effective against yeasts, molds and common soft drink spoilage bacteria. The minimum inhibitory concentration (MIC) for benzoic acid varies according to the microorganism and according to the composition and nutrient content of the test system (liquid media) or the food or beverage. (Table 1). Additionally, variation on the MIC is observed for resistant yeasts (Table 2).

When either benzoic acid or benzoate salts are added to an aqueous solution, both the undissociated benzoic acid [HA] and the dissociated benzoate [A^-] are present.[3]/[25]/ The undissociated form of benzoic acid is largely, if not entirely, related to its anti-microbial activity. Therefore, the undissociated form is also known as "active form".

Table 1. Antimicrobial Spectrum of Benzoic Acid Against Selected Bacteria/Yeasts/Fungi. [2]/

Microorganisms	**pH**	**MIC (ppm)** [a]
Bacteria		
Lactobacillus sp.	4.3-6.0	300-1,800
Yeasts		
Sporogenic yeasts	2.6-4.5	20-200
Asporogenic yeasts	4.0-5.0	70-150
Candida krusei	-	300-700
Pichia membranefaciens	-	700

Rhodotorula sp.	-	100-200
Saccharomyces cerevisiae	4.0	600
Fungi		
Aspergillus sp	3.0-5.0	20-300
Aspergillus niger	5.0	2,000
Byssochamys nivea	3.3	500
Penicillium citrinum	5.0	2,000
Penicillium glaucum	5.0	400-500

[a]MIC in µg/mL (ppm)

Table 2: Minimum Inhibitory Concentrations of Benzoic Acid for Yeasts **[2]/**

Isolate[b]	**MIC (ppm)**
Candida krusei	440
Hansenula anomala	223
Kloeckera apiculata	188
Kluveromyces fragilis	173
Saccharomyces cerevisiae	170-450
Saccharomyces ludwigii	500-600
Zygosaccharomyces bailii	600-1,300
Zygosaccharomyces bisporus	200-350
Zygosaccharomyces rouxii	242-330

[b] Most were isolated from spoiled foods that already contained preservatives. Isolates were grown at 25°C, pH 3.5.

Undissociated forms of antimicrobial organic acids are more hydrophobic and have increased effectiveness as a direct antimicrobial agent.[26]/ Hydrophobic acid molecules interact with the lipid microbial cell wall to disrupt microbial activity. The hydrophobicity of undissociated acid forms is typically measured by the logarithm of the octanol/water partition coefficient. Due to its higher hydrophobicity, benzoic acid is the most potent food anti-microbial agent even in comparison to sorbates (Table 3).

Table 3. Log (octanol/water partition coefficient) of undissociated organic acids. [26]/

Organic Acid Preservatives	**Log (octanol/water partition coefficient)**
Benzoic Acid	1.87
Sorbic Acid	1.70

The equilibrium between the undissociated (HA) and dissociated (A^-) benzoic acid is dependent on pH. A formulation with pH 4.18 is found to contain equal concentrations of the dissociated and undissociated species of benzoic acid (Figure 1). However, there is a 1:2 ratio of benzoic acid (HA): (A^-) at pH 4.5 while as much as 94% HA exists at pH 3.0. Figure 1 clearly defines the effect of pH on the concentration of the undissociated (active) form of benzoic acid.

Figure 1. Undissociated Benzoic Acid (Active Form) at Various pH Values. [2]/

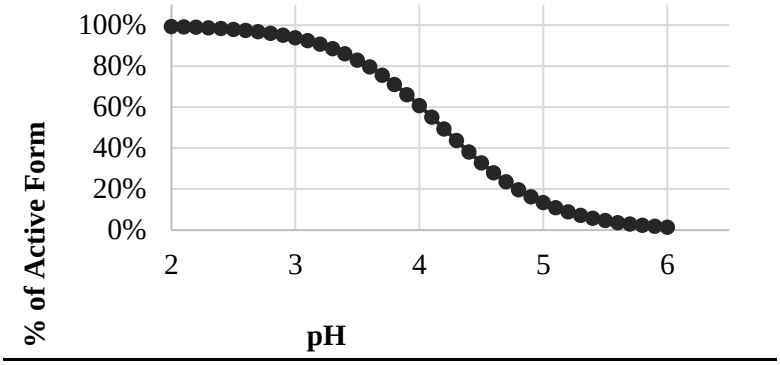


Table 4 tabulates data in Figure 1 representing the ratios of undissociated and dissociated acid for solutions with differing pH. These ratios enable calculation of the active form concentration. For example, levels of the active form in a solution at pH 3.5 with 250 ppm of benzoic acid would equate to levels in a solution with 475 ppm of benzoic acid at pH 4.3. For the same microorganism, as pH increases the MIC for benzoic acid also increases (Table 5). Therefore, in beverages with higher pH, levels of benzoates should be increased to compensate for losses in the active form of benzoic acid. From a practical standpoint, the ability to reduce the equilibrium pH of a beverage or food below approximately pH 2.8 is limited because the taste profile generally becomes so tart/sour that it is no longer acceptable to consumers or suitable for commercial sale.

Table 4. Undissociated Proportions of Benzoic at Various pH Ranges. [2]/

	Benzoic Acid	
pH	HA	A^-
2.0	99.4%	0.6%
2.1	99.2%	0.8%
2.2	99.0%	1.0%
2.3	98.7%	1.3%
2.4	98.4%	1.6%
2.5	98.0%	2.0%
2.6	97.5%	2.5%
2.7	96.9%	3.1%
2.8	96.1%	3.9%
2.9	95.1%	4.9%
3.0	93.9%	6.1%
3.1	92.5%	7.5%
3.2	90.7%	9.3%
3.3	88.6%	11.4%
3.4	86.0%	14.0%
3.5	83.0%	17.0%
3.6	79.6%	20.4%

3.7	75.6%	24.4%
3.8	71.1%	28.9%
3.9	66.1%	33.9%
4.0	60.8%	39.2%
4.1	55.2%	44.8%
4.2	49.4%	50.6%
4.3	43.7%	56.3%

HA = Undissociated Form A^- = Dissociated form

Table 5. Effect of Benzoic Acid on the Growth of Important Spoilage Yeasts at Different pH [2]/

	Maximum Concentration (mg/L) Allowing Growth			
Yeast	**pH 2**	**pH 3**	**pH 5**	**pH 7**
Kloeckera apiculata	NG2	NG2	750	1,200
Pichia membranefaciens	NG2	NG2	750	1,200
Saccharomyces cerevisiae	NG1	NG2	750	1,200
Zygosaccharomyces bailii	NG1	NG2	1,200	NG1
Zygosaccharomyces rouxii	NG1	NG2	750	1200

Note: NG1, no growth in absence of benzoic acid; NG2 - no growth in presence of 250 mg/L of benzoic acid.

Based on Tables 1, 2 and 5, MIC levels of benzoic acid adequate to perform preservative function against various microorganisms for beverages with pH lower or equal to 3.5 range anywhere between 20 – 250 ppm as benzoic acid. For beverages with pH higher than 3.5, increased levels are needed. Considering the dissociation ratio for benzoic acid (Table 4), the adequate level of protection for beverages with pH between 3.6 and 4.3 is 500ppm.

Sodium benzoate is usually preferred for use in beverages due to its great solubility. The sodium salt of benzoic acid is approximately 240 times more soluble in water than benzoic acid.[11]/ Also, sodium benzoate has better solubility than potassium sorbate. While 1g of potassium sorbate is soluble in 4.5ml of water, the same amount of sodium benzoate is soluble in 2ml of water. In simple water solution, the different solubility of sodium benzoate and potassium sorbate may not be that important. [27]/[28]/ However, in complex formulations saturated with other ingredients small differences in solubility have a major impact. This explains sodium benzoate's better performance during the manufacturing process of beverages generally and in concentrates specifically. In addition, certain spoilage microrganisms of industrial significance (e.g., *Glocunobacter* spp. and certain *Aspergillus* spp.) are quite resistant to sorbate, thus limiting its value as a stand-alone preservative agent.

Conclusion

Benzoates continue to be a particularly important part of optimal preservative systems for water-based flavored drinks due to their safety, performance characteristics and minimal impact to product taste. Using benzoates in beverages lengthens the shelf-life and minimizes unnecessary food losses caused by microbial growth. The use of benzoates in concert with other "hurdles" allows certain high acid (less than pH 4.6), shelf-stable beverages to be produced using lower cost beverage processing equipment, which in turn expands their availability in developing countries

and the jobs created by local manufacturing. Levels needed depend on the beverage type, degree of carbonation, sensory properties, packaging and the inherent microbiological stability of a particular beverage product. Different production environments, transportation conditions, storage conditions, climatic conditions and national regulatory food additives frameworks all contribute to the varying preservative systems and use levels around the world. Nevertheless, only the lowest possible levels necessary to maintain product integrity are used.

Thus, the use of benzoates is advantageous in beverage products and technologically justified to ensure preservation of beverage quality, enhanced beverage shelf-life and reduction in yeast, molds and bacterial growth.

References

[1]/ WAREING, P.; DAVENPORT, R. R. Microbiology of soft drinks and fruit juices. In: Chemistry and Technology of Soft Drinks and Fruit Juices. 3rd edition. Wiley-Blackwell, 2016.

[2]/ CHIPLEY, J. R. Sodium benzoate and benzoic acid. In: Antimicrobials in Food. 3rd edition. Taylor & Francis Group, LLC, 2005.

[3]/ LINDSAY, R. C. Food additives. In: Food Chemistry. 3rd edition. Marcel Dekker, Inc., 1996.

[4]/ MORROW, R. S.; QUINN, C. M. Carbonated beverages. In: Kirk-Othmer Encyclopedia of Chemical Technology. John Willey & Sons, 2007.

[5]/ PITT, J. I.; HOCKING, A. D. Fungi and Food Spoilage. Springer Science + Business Media, LLC, New York, 2009.

[6]/ Phillips, G.F. and J.G. Woodroof. 1981. Beverage acids, flavors, colors and emulsifiers. In: *Carbonated and Noncarbonated Beverages* (Woodroof, J.G. and G.F. Phillips, eds.) AVI Publishing Co., Inc., Westport, CT. pp. 152-207.

[7]/ Lindsay, R.C. 1985. Food Additives. In: *Food Chemistry* (O.R. Fennema, ed.) Marcel Dekker, Inc. New York pp. 629-688.

[8]/ Monsanto Product Bulletin. (Not dated). *The Safe Preservation of Food with Monsanto Benzoic Acid and Sodium Benzoate.* Monsanto Chemical Co, St. Louis, MO.

[9]/ 21CFR113.3(n); 21CFR114.3(a); 21CFR114.3(b)

[10]/ LAWLOR, K. A.; SCHUMAN, J. D.; SIMPSON, P. G.; TAORMINA, P. J. Microbiological Spoilage of Beverages. In: Compendium of the Microbiological Spoilage of Foods and Beverages. Springer Science+Business Media, 2009.

[11]/ DAVIDSON, P. M.; TAYLOR, T. M.; SCHMIDT, S. E. Chemical preservatives and natural antimicrobial compounds. In: Food Microbiology: Fundamentals and Frontiers, 4th edition. ASM Press, 2013.

[12]/ SOMOGYI, L. P. Food Additives. In: Kirk-Othmer Encyclopedia of Chemical Technology. John Willey & Sons, 2015.

[13]/ DAVIDSON, P. M.; BRANEN, A.L. Food Antimicrobials – An Introduction. In: Antimicrobials in Food. 3rd edition. Taylor & Francis Group, LLC, 2005.

[14]/ Mira, N.P., M.C. Teixeira and I. Sa-Correia. 2010. Adaptive response and tolerance to weak acids in *Saccharomyces cerevisiae*: A genome-wide view. Journal of Integrative Biology. 14(5): 525-540.

[15]/ Van Der Meer, J. R., W.M. de Vos, S. Harayama and A.J.B. Zehnder. 1992. Molecular mechanisms of genetic adaptation to xenobiotic compounds. *Microbiological Reviews.* 56(4): 677-694.

[16]/ Andersson, D.I. and D. Hughes. 2012. Evolution of antibiotic resistance at non-lethal drug concentrations. *Drug Resistance Updates.* 15: 162-172.

[17]/ Richards, T. A., G. Leonard, D. M. Soanes and N. J. Talbot. 2011. Gene transfer into the fungi. *Fungal Biology Reviews.* 25: 98-110.

[18]/ Long, M., E. Betran, K. Thornton and W. Wang. 2003. The origin of new genes: Glimpses from the young and old. Nature Reviews Genetics. 4: 865-876.

[19]/ Schmidt-Heydt, M., E. Baxter, R. Geisen and N. Magan. 2007. Physiological relationship between food preservatives, environmental factors, ochratoxin and *otapks*PV gene expression by *Penicillium verrucosum*. *International Journal of Food Microbiology*. 119: 277-283.

[20]/ Arroyo, M., D. Aldred and N. Magan. 2005. Environmental factors and weak organic acid interactions have differential effects on control of growth and ochratoxin A production by *Penicillium verrucosum* isolates in bread. *Int. J. Food Microbiol.* 98, 223–231.

[21]/ Gareis, M., J. Bauer, A. von Montgelas and B. Gedek. 1984. Stimulation of Aflatoxin B1 and T2-Toxin production by sorbic acid. *Applied and Environmental Microbiology*. 47(2): 416-418.

[22]/ Mann, D.A. and L.R. Beuchat. 2008. Combinations of antimycotics to inhibit the growth of molds capable of producing 1,3-pentadiene. *Food Microbiology*. 25: 144-153.

[23]/ Kinderlerer, J.L. and P.V. Hatton. 1990. Fungal metabolites of sorbic acid. *Food Additives and Contaminants.* 7(5): 657-669.

[24]/ A summary of human feeding studies by three independent research organizations was published in a book titled, "USDA Report No. 88."

[25]/ OPGRANDE, J.L; BROWN, E.E; HESSER, M.; ANDREWS, J. Benzoic Acid. In: Kirk-Othmer Encyclopedia of Chemical Technology. John Willey & Sons, 2003.

[26]/ 2003 International Society of Beverage Technologists (ISBT) Beverage Acidulant Manual.

[27]/ REILLY JR., W. J. Pharmaceutical Necessities. In: Remington The Science and Practice of Pharmacy. 21st ed. Lippincott Williams & Wilkins, 2006.

[28]/ USP. Sodium Benzoate Monograph. In: Food Chemical Codex. 10th ed. U.S. Pharmacopeial Convention, 2016.

Appendix II - Market Penetration of Benzoate Containing Products

Methodology

The Beverage Marketing Corporation (BMC) culled market share data for the following markets in which the largest proportion of benzoate-containing beverage products exist – U.S.A., Canada, Brazil and Mexico. Volume data in millions of gallons were obtained for the entire liquid refreshment beverage (LRB) category which consists of the following 10 beverage types:

- Diet carbonated soft drinks
- Regular carbonated soft drinks
- Juice drinks
- 100% juice
- Non-carbonated water-based flavored drinks
- Energy drinks
- Sports drinks
- RTD teas
- RTD coffees
- Bottled Water

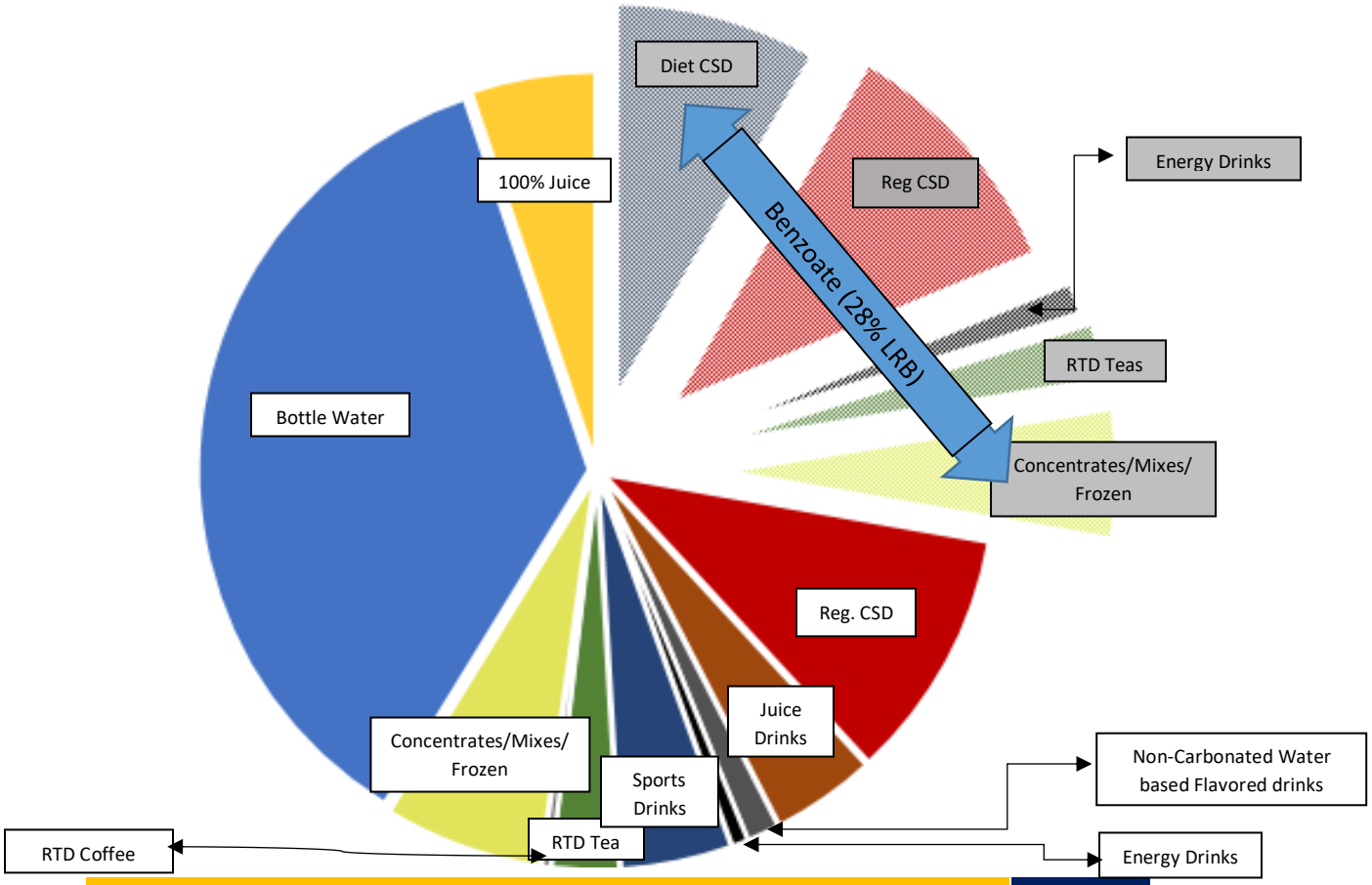
The top selling brands within each "beverage type" - making up anywhere from 70-90% of the entire market for that "beverage type" - were identified. An "all other" category was created within each "beverage type" to capture the remaining beverages in the bottom 10-30% of the market. Determination of whether brands contained or did not contain benzoates was based on:

- Ingredient label statements accessible on company websites;
- Canadean database;
- Mintel database; and
- Directly from companies.

The following worst-case scenario assumptions were made to create the below pie charts:

- Ambiguous "Other Private Label" entries were assumed to contain benzoates;
- Products that have been discontinued in 2016 were assumed to contain benzoates (for the purpose of aligning with the 2015 market share data);
- Products for which information was not provided were assumed to contain benzoates (unless good justification existed based on the other brands within the particular "beverage type" that no benzoates are typically used in that category – e.g., 100% fruit juice);
- Within each market and within each "beverage type" category there is a list of brands that takes up about 80% or so of that market share and the remaining 20% or so is captured together as "All Other". Thus, the assumption was that the same distribution of benzoate-containing products seen for 80% of the market would be the same for the 20% "All Other" entry;
- For "concentrates", it was assumed the distribution of benzoate-containing products across relevant RTD beverage types (i.e., CSDs, 100%fruit juice, juice drinks) in the respective markets was the same for the "concentrates" category.

USA 2015 Refreshment Beverage Market
(27.8% consists of benzoate-containing products)



Category	U. S. A. % LRB
Packaged Diet CSD containing benzoate	8.0
Packaged Reg CSD containing benzoate	10.0
Non-Carbonated Water Based Flavor Drinks containing benzoates	0.0
Energy Drinks containing benzoates	1.0
RTD Teas with benzoates	2.0
Concentrates/Mixes/Frozen** containing benzoate	5.0
Sub Total (benzoate only)	27.0
Packaged Reg CSD	10.0
Juice Drinks*	4.0
Non-Carbonated Water Based Flavor Drinks	1.0
Energy Drinks	0.0
Sports Drinks	4.0
RTD Tea	2.0
RTD Coffee	0.0
Concentrates/Mixes/Frozen**	6.0
Bottled water	36.0
100% Juice*	5.0
Sub Total (no benzoates)	72.0
Total Volume (benzoate + non-benzoate)	100.0

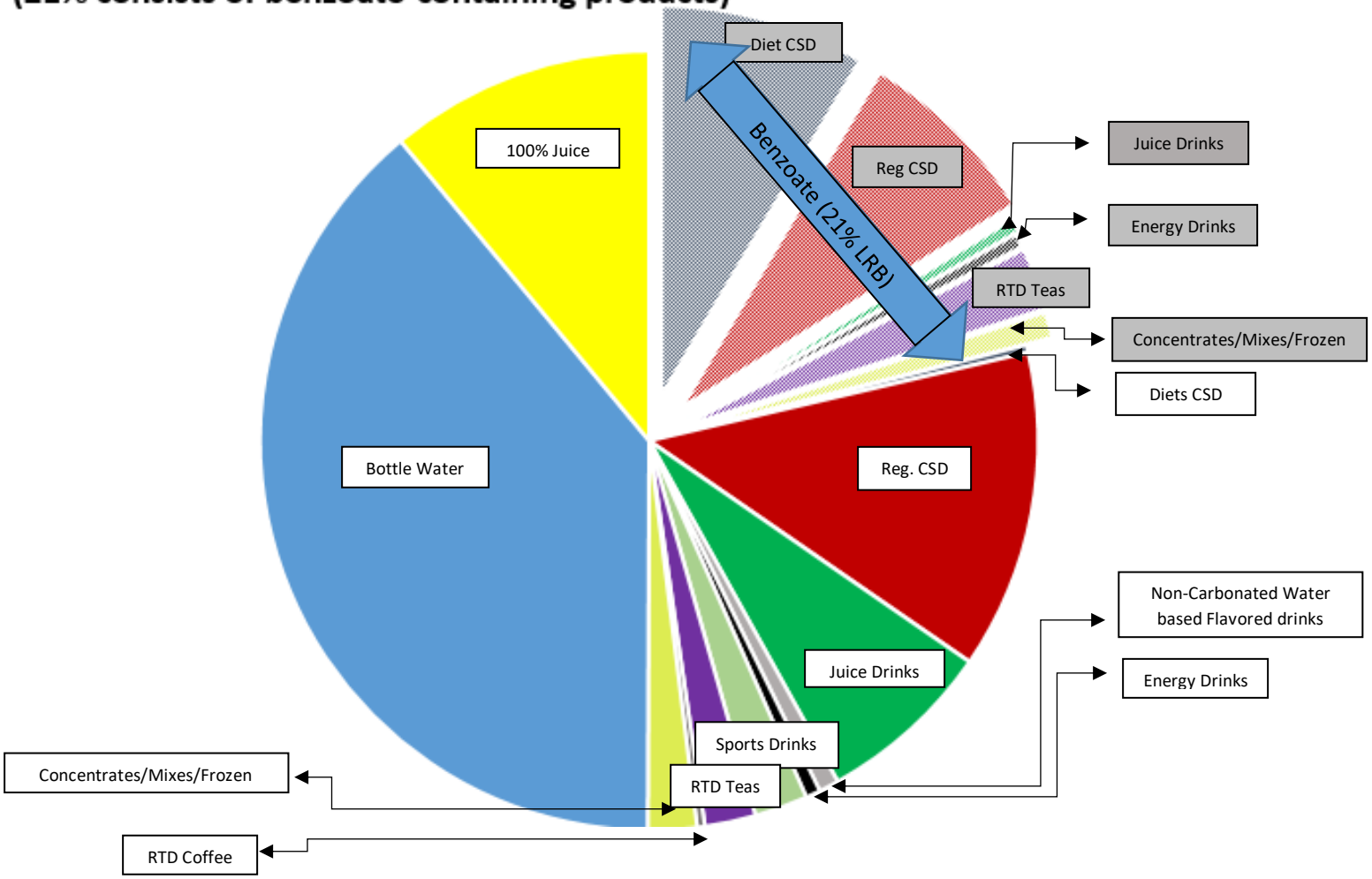
* Excludes concentrates

** Includes fountain CSDs, concentrate juices and juice drinks, and powdered fruit mixes

Source: Beverage Marketing Corp., Canadean

Please Note: Beverages with pH > 3.5 take up 1.71% of the LRB market

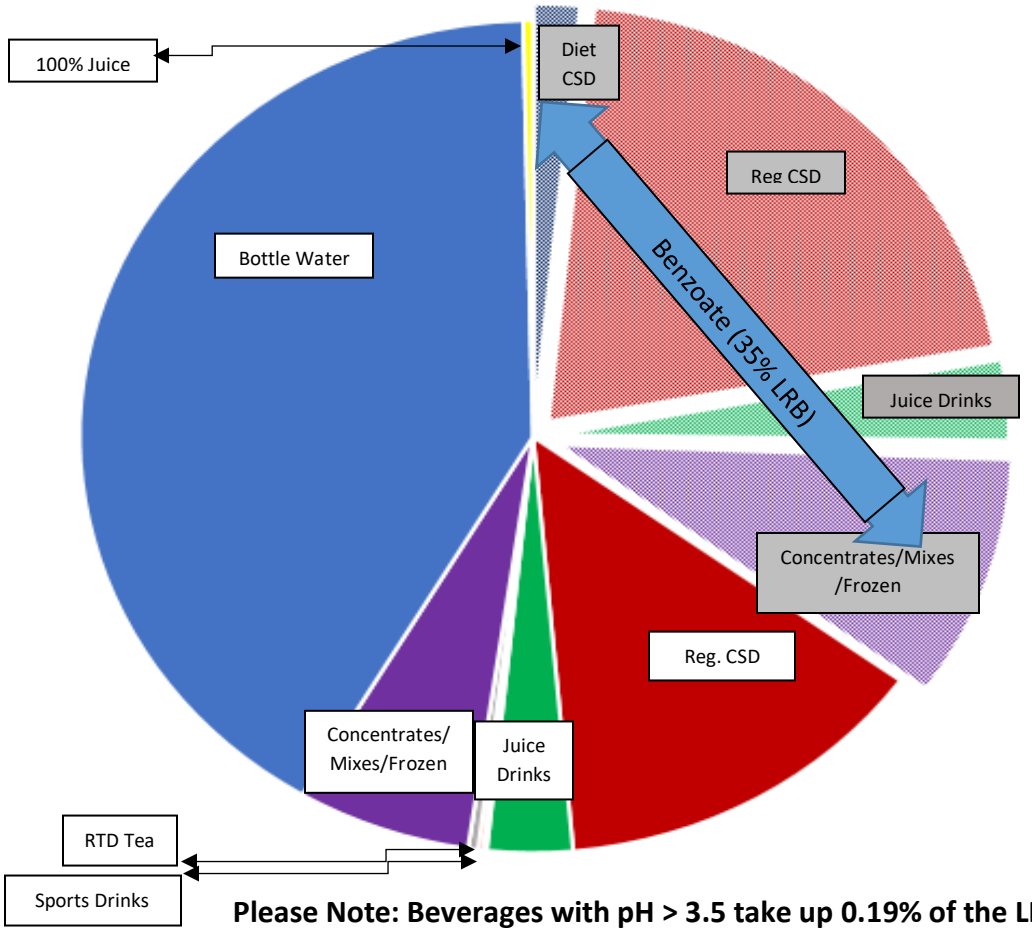
Canada 2015 Refreshment Beverage Market
(21% consists of benzoate-containing products)



Please Note: Beverages with pH > 3.5 take up 2.40 % of the LRB market.

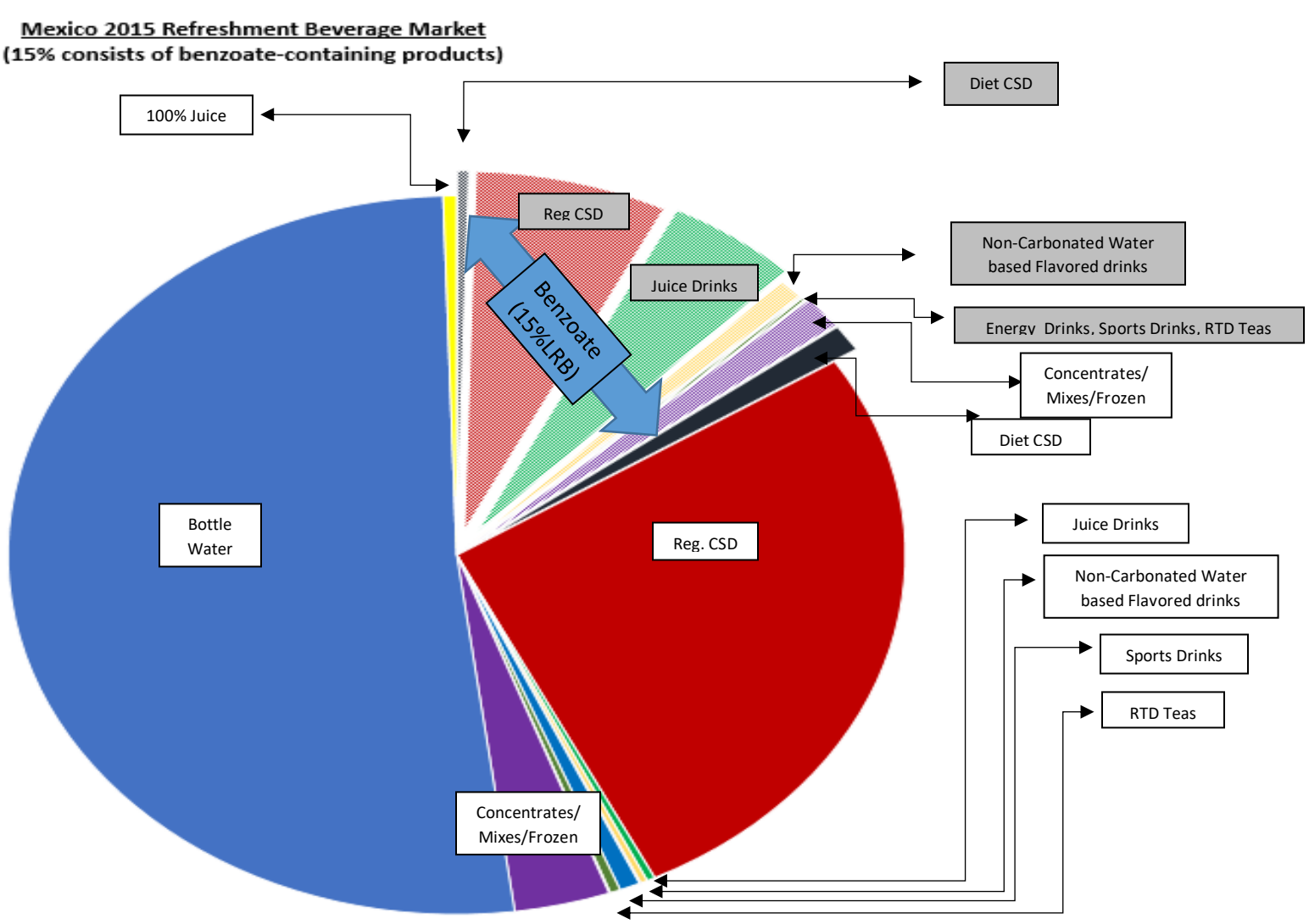
Category	Canada % LRB
Packaged Diet CSD containing benzoate	8.0
Packaged Reg CSD containing benzoate	7.0
Juice Drinks containing benzoates	0.0
Energy Drinks containing benzoates	0.0
Sports Drinks containing benzoates	0.0
RTD Teas with benzoates	2.0
Concentrates/Mixes/Frozen** containing benzoate	1.0
Sub Total (benzoate only)	21.0
Packaged Diet CSD	0.0
Packaged Reg CSD	13.0
Juice Drinks*	7.0
Non-Carbonated Water Based Flavor Drinks	0.0
Energy Drinks	0.0
Sports Drinks	2.0
RTD Tea	2.0
RTD Coffee	0.0
Concentrates/Mixes/Frozen**	2.0
Bottled water	38.0
100% Juice*	11.0
Sub Total (no benzoates)	78.0
Total Volume (benzoate + non-benzoate)	100.0

Brazil 2015 Refreshment Beverage Market
(35% consists of benzoate-containing products)



Please Note: Beverages with pH > 3.5 take up 0.19% of the LRB market.

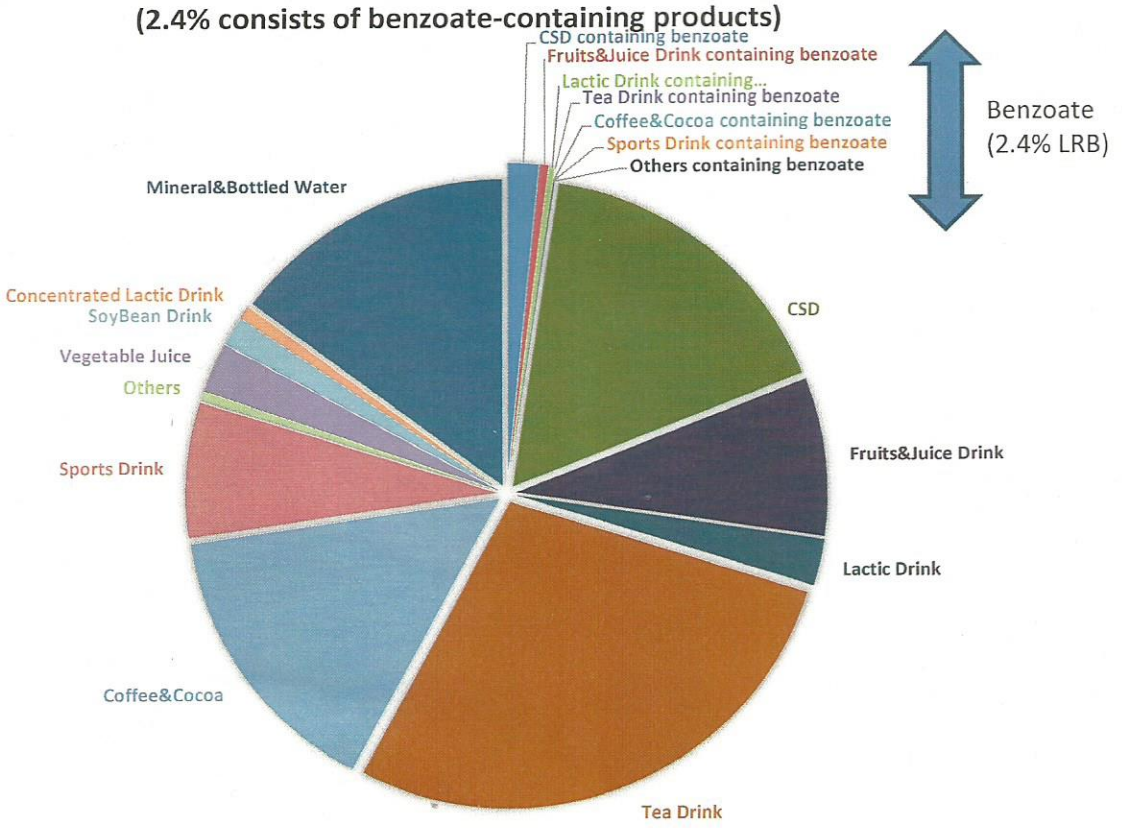
Category	Brazil % LRB
Packaged Diet CSD containing benzoate	1.0
Packaged Reg CSD containing benzoate	20.0
Juice Drinks containing benzoates	3.0
Non-Carbonated Water Based Flavor Drinks containing benzoates	0.0
Energy Drinks containing benzoates	0.0
Sports Drinks containing benzoates	0.0
RTD Teas with benzoates	0.0
Concentrates/Mixes/Frozen** containing benzoate	9.0
Sub Total (benzoate only)	34.0
Packaged Diet CSD	0.0
Packaged Reg CSD	13.0
Juice Drinks*	3.0
Non-Carbonated Water Based Flavor Drinks	0.0
Energy Drinks	0.0
Sports Drinks	0.0
RTD Tea	0.0
RTD Coffee	0.0
Concentrates/Mixes/Frozen**	6.0
Bottled water	41.0
100% Juice*	0.0
Sub Total (no benzoates)	65.0
Total Volume (benzoate + non-benzoate)	100.0



Please Note: Beverages with pH > 3.5 take up 0.09 % of the LRB market.

Category	Mexico % LRB
Packaged Diet CSD containing benzoate	0.0
Packaged Reg CSD containing benzoate	6.0
Juice Drinks containing benzoates	4.0
Non-Carbonated Water Based Flavor Drinks containing benzoates	0.0
Energy Drinks containing benzoates	0.0
Sports Drinks containing benzoates	0.0
RTD Teas with benzoates	0.0
Concentrates/Mixes/Frozen** containing benzoate	1.0
Sub Total (benzoate only)	14.0
Packaged Diet CSD	1.0
Packaged Reg CSD	26.0
Juice Drinks*	0.0
Non-Carbonated Water Based Flavor Drinks	0.0
Energy Drinks	0.0
Sports Drinks	0.0
RTD Tea	0.0
RTD Coffee	0.0
Concentrates/Mixes/Frozen**	3.0
Bottled water	51.0
100% Juice*	0.0
Sub Total (no benzoates)	85.0
Total Volume (benzoate + non-benzoate)	100.0

Japan 2015 Refreshment Beverage Market
(2.4% consists of benzoate-containing products)



Category	Japan LRB
CSD containing benzoate	1.60%
Fruits&Juice Drink containing benzoate	0.44%
Lactic Drink containing benzoate	0.27%
Tea Drink containing benzoate	0.01%
Coffee&Cocoa containing benzoate	0.01%
Sports Drink containing benzoate	0.00%
Others containing benzoate	0.06%
SubTotal (benzoate only)	2.39%
CSD	16.62%
Fruits&Juice Drink	8.40%
Lactic Drink	2.43%
Tea Drink	28.02%
Coffee&Cocoa	14.83%
Sports Drink	7.19%
Others	0.46%
Vegetable Juice	2.60%
SoyBean Drink	1.51%
Concentrated Lactic Drink	0.70%
Mineral&Bottled Water	14.85%
SubTotal (no benzoates)	97.61%
Total Volume (benzoate + no benzoates)	100.00%

Source: JSDA

Appendix III: Estimated Exposure to Benzoates from Non-Alcoholic Beverages in the U.S., Canada, Mexico and Brazil Based on Updated Reported Use Levels in 2016

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11 November 2016

Estimated Exposure to Benzoates from Non-Alcoholic Beverages in the U.S., Canada, Mexico and Brazil Based on Updated Reported Use Levels in 2016

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Estimated Daily Intake of Benzoates from Non-Alcoholic Beverages in the U.S., Canada, Mexico and Brazil Based on Updated Reported Use Levels in 2016

1.0 INTRODUCTION

In 2014, the International Council of Beverages Association (ICBA) submitted brand-specific use levels and dietary exposure estimates for benzoates in non-alcoholic beverages [Codex General Standard for Food Additives (GSFA) Category 14.1] to the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in response to a call for data to determine daily intake levels.

Use level information was provided for 6 countries in which the national maximum limit was greater than 400 mg/L, and dietary exposure assessments were conducted for 4 of these countries. These exposure assessment models utilized information on national consumption of non-alcoholic beverages in each jurisdiction, along with the maximum reported - and in some cases assumed - use level for each beverage category.

JECFA reviewed the exposure assessment models at the 80th meeting (JECFA, 2016), and concluded that the exposure results submitted were not appropriate for assessment based on the inclusion of maximum, rather than average, typical use levels. JECFA subsequently conducted their own series of exposure assessments based on the FAO/WHO Chronic Individual Food Consumption Database – Summary Statistics (CIFOCOss) database (only beverages) and evaluated published estimates of total dietary exposure to benzoates (including non-beverages use). The mean exposure levels from non-alcoholic beverages estimated using the FAO/WHO CIFOCOss database, combined with average typical use levels of benzoates, were determined to range between 0.1 and 4.1 mg/kg body weight/day, and the 95th percentile exposure levels ranged from 0.2 to 10.9 mg/kg body weight/day (notably the highest level was estimated for the 97.5th percentile). Data from the published literature identified mean intakes of 0.04 to 1.5 mg/kg body weight/day, and 95th percentile intakes of 0.2 to 3.9 mg/kg body weight/day from the total diet for the general population. When the consumers-only dataset were considered, the mean intake estimates ranged from 0.1 to 6.8 mg/kg body weight/day, and 0.7 to 9.0 mg/kg body weight/day at the 95th percentile. As part of the evaluation, it was noted by the Committee that the largest contributions to total estimated dietary exposure to benzoates were from non-alcoholic beverages, up to 80% in Brazil.

Following on from the publication of this report and a recommendation to consider the feasibility of reducing the maximum limit (ML) from beverages, the 48th Session of the Codex Committee of Food Additives (CCFA48) applied an interim ML of 250 mg/L to category 14.1.4 *Water-based*

flavoured drinks, including "sport," "energy," or "electrolyte" drinks and particulated drinks (Codex Alimentarius Commission, 2016).

The ICBA has compiled an impact assessment of the anticipated effect of this reduction in the ML – and any further hypothetical reductions – for water-based beverages in various markets (please refer to ICBA's comment in response to the First Circular). In addition, the use levels submitted by members in 2014 have been reviewed and updated to align with current market share data for the key product categories. The ICBA has organized a re-evaluation of exposure to this food additive in four jurisdictions for which the national limits exceeded 400 ppm, and in which there was determined to be significant market disruption to benzoate-containing beverages at or below an ML of 250 ppm [United States (U.S.), Canada, Mexico and Brazil]. This was undertaken in order to incorporate updated use level information and more realistic assumptions regarding potential exposure to this food additive. These refined exposure assessments focus on the 'average' as opposed to the 'maximum' typical use level, and also consider market share information, incorporating a factor to consider presence probability or occurrence into the model (*i.e.*, whether the additive is present in the specific beverage type). More details on the individual models are discussed in Section 2.0, and the results for each individual country are discussed in the sections thereafter.

The inclusion of up-to-date and brand-specific use level data for products which account for a large proportion of the respective markets is recognized as a key strength of the current work. While it is noted that in JECFA's most recent assessment of benzoate exposure, described above, utilized values for the average use level submitted by industry, these levels were not weighted according to their market share within the regions of interest, and as such, use levels for brands which are consumed infrequently contribute equally to the final exposure estimates as products which have a higher market penetration. Furthermore, the CIFOCOss database is comprised of summary statistics for 'consumers only'. While the use of summary statistics from the CIFOCOss database is a valuable screening tool for risk evaluation, it does not permit the calculation of dietary exposure estimates at the level of the individual consumer to provide information on the full distribution of intakes for a population group. Further, the inclusion of summary statistics in the calculation of exposure does not permit the inclusion of a wide range of potential use levels of a food additive within a food/beverage category. Indeed, based on the benzoate use level collection efforts in 2016, the individual concentration data points received from beverage manufacturers indicate a dispersed range of potential use levels even within a single GSFA food category (*i.e.*, *14.1.4 Water-based flavored drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks*).

Therefore, the work described herein is intended to provide a more accurate, up-to-date, and sophisticated estimate of exposures to benzoates from the largest contributing sector, non-alcoholic beverages, as a subsequent tier to the work conducted by JECFA at the 80th meeting in 2015 (JECFA, 2016). The estimates described herein are intended to complement

the estimates already published and to be considered in the context of establishing an ML for benzoate use.

2.0 REFINED EXPOSURE MODELS

2.1 Updated Use Level Data

As mentioned in the Introduction, ICBA has re-examined use level data submitted to JECFA in 2014 and identified anomalies (issues included not converting uses to benzoate equivalents and miscategorizing some of the beverage products – *e.g.*, juice drinks placed under fruit juices erroneously). As such, the program to collate benzoate use levels was re-initiated, focusing on the category '*water-based flavoured drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks*' (Codex GSFA category 14.1.4) as well as 100% fruit juices. Market share information was purchased by the Beverage Marketing Corporation (BMC) and Canadean detailing the volume in millions of gallons of the top contributing brands for the following 'water-based flavoured drink' sub-categories:

- Regular carbonated soft drinks;
- Diet carbonated soft drinks;
- Flavored water;
- Fruit juice-based drinks;
- Energy drinks;
- Sports drinks;
- Ready-to-drink (RTD) tea;
- RTD coffee; and
- 100% juice[1].

Use level data and information on pH was supplied for all branded products containing benzoates by individual manufacturers, and complemented by Mintel datasets as needed. Data (both market share and use level/pH) were specified for each jurisdiction. In instances where brand-specific concentration information were not submitted to the ICBA, the market share for the remaining brands for which there were concentration data available were re-distributed to that particular product.

Table 2.1-2 summarizes the use level data collected for all non-alcoholic beverage categories in 2014 and 2016 for all 4 jurisdictions considered in the current dietary exposure assessment (note: benzoate use levels were not gathered for Canada in 2014). It is noted that the focus of the 2016 data collection was placed on categories 14.1.2.1 (Fruit juice) and 14.1.4 (Water-based flavored drinks) as occurrence data for the other beverage categories were

[1] Although this is not one of the 14.1.4 sub-categories, fruit juices were determined to be a main contributor to benzoate exposure based on 100% assumed occurrence (see 2014 report); however due to concern regarding incorrect categorisation of these products in the 2014 data collection, it was deemed relevant to collate new data on this beverage category.

considered well understood based on the consensus of data collected in 2014 and supplemented by correspondence with ICBA members and other databases (*i.e.,* Mintel).

A similar range of use levels – with exceptions noted – were reported for category 14.1.4 (Water-based flavored drinks) in both of the data collection programs. Information on the pH of beverages were included in the 2016 data collection efforts due to an expressed intent by the ICBA to recommend that the maximum use of benzoates accommodate a higher limit of 500 mg/kg for beverages with a pH greater than 3.5. As such, the use levels of benzoates received by ICBA members were stratified according to pH, where appropriate (as described in the sections that follow, this information has been incorporated into the assessment models to consider the impact of such a recommendation on anticipated exposure levels).

The most notable difference between the two data collection programs for any individual GSFA food category was identified for category 14.1.2.1 (Fruit juice) in the U.S., wherein there were a range of use levels reported in 2014, however in the 2016 data collection, only values indicating non-occurrences were received. It is understood that this discrepancy was due to an incorrect categorization of fruit juice-based drinks (falling under the remit of 14.1.4) as 100% fruit juices in 2014. Based on this, a use level of 0 ppm was considered appropriate and more accurate for category 14.1.2.1 (Fruit juice) and concentrates thereof (14.1.2.3 Concentrates for fruit juice).

Use levels were not collated for categories 14.1.3.1 (Fruit nectar), 14.1.3.3 (Concentrates for fruit nectars), and 14.1.3.4 (Concentrates for vegetable nectars) in 2016. Based on the general consensus of the data available and correspondences with ICBA members, it was evident that benzoate use within this category was uncommon and non-existent, even though uses were reported for Brazil only in 2014 likely due to similar miscategorizations as noted above.

Use level data was not collated for category 14.1.5 (Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages excluding cocoa) in 2016, similar to the general consensus of the 2014 data collection which indicated that benzoates are not used in these product types. ICBA members confirmed that this was accurate of typical practices for these product types.

Table 2.1-1 Summary of Use Level Data Gathered on Benzoates for Non-Alcoholic Beverage GSFA Food Categories

Country	GSFA Food Category	Range of Reported Use Levels (ppm) in 2014	Range of Typical Reported Use Levels (ppm) in 2016
United States	14.1.2.1 Fruit Juice	0 to 229	0
	14.1.2.3 Concentrates for Fruit Juice	0 to 168	-
	14.1.3.1 Fruit Nectar	0[1]	-
	14.1.3.3 Concentrates for Fruit Nectar	0[1]	-
	14.1.3.4 Concentrates for Vegetable Nectars	na[2]	-

Table 2.1-1 Summary of Use Level Data Gathered on Benzoates for Non-Alcoholic Beverage GSFA Food Categories

Country	GSFA Food Category	Range of Reported Use Levels (ppm) in 2014	Range of Typical Reported Use Levels (ppm) in 2016
	14.1.4 Water-Based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	0 to 627	0 to 367 (pH≤3.5); 150 to 428.3 (pH>3.5)
	14.1.5 Coffee, Coffee Substitutes, Tea, Herbal Infusions, and Other Hot Cereal and Grain Beverages, Excluding Cocoa	0	-
Canada	14.1.2.1 Fruit Juice	nc	0
	14.1.2.3 Concentrates for Fruit Juice	nc	-
	14.1.3.1 Fruit Nectar	nc	-
	14.1.3.3 Concentrates for Fruit Nectar	nc	-
	14.1.3.4 Concentrates for Vegetable Nectars	nc	-
	14.1.4 Water-Based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	nc	0 to 314 (pH≤3.5); 11 to 438 (pH>3.5)
	14.1.5 Coffee, Coffee Substitutes, Tea, Herbal Infusions, and Other Hot Cereal and Grain Beverages, Excluding Cocoa	nc	-
Mexico	14.1.2.1 Fruit Juice	0[4]	0
	14.1.2.3 Concentrates for Fruit Juice	na[4]	-
	14.1.3.1 Fruit Nectar	0[1]	-
	14.1.3.3 Concentrates for Fruit Nectar	na[1]	-
	14.1.3.4 Concentrates for Vegetable Nectars	0[1]	-
	14.1.4 Water-Based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	0 to 368	0 to 300 (pH≤3.5); 142 to 200 (pH>3.5)
	14.1.5 Coffee, Coffee Substitutes, Tea, Herbal Infusions, and Other Hot Cereal and Grain Beverages, Excluding Cocoa	0	-
Brazil	14.1.2.1 Fruit Juice	na	0
	14.1.2.3 Concentrates for Fruit Juice	na	0
	14.1.3.1 Fruit Nectar	0 to 339	0[3]
	14.1.3.3 Concentrates for Fruit Nectar	na	-
	14.1.3.4 Concentrates for Vegetable Nectars	na	-
	14.1.4 Water-Based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	0 to 371	0 to 366 (pH≤3.5); 60 to162 (pH>3.5)
	14.1.5 Coffee, Coffee Substitutes, Tea, Herbal Infusions, and Other Hot Cereal and Grain Beverages, Excluding Cocoa	0	-

GSFA = General Standard for Food Additives; na = not available (no data submitted by ICBA members); nc = not collected (Canadian benzoate use levels was not gathered in 2014).
"-" = category not included in the 2016 use level data collection program (limited to categories 14.1.2.1 and 14.1.4).
[1] A use level of 339 ppm was applied to this category for the 2014 intake assessment.
[2] The maximum permitted level of 1,000 ppm was utilized for this category for the 2014 intake assessment.
[3] Value was obtained in 2016.
[4] A use level of 229 ppm was utilized for this category in the 2014 intake assessment.

2.2 Updated Exposure Assessment Models

Table 2.2-1 below presents the main assumptions and data types for both the 2014 and 2016 exposure models for all four countries included in the current assessment. This identifies the new assumptions incorporated into the models in order to obtain a more realistic estimate of exposure by the population cohorts.

When conducting exposure estimates, three main types of methodology may be considered based on the availability of chemical occurrence and food consumption data, namely deterministic, distributional and probabilistic (Kroes *et al.*, 2002; ILSI, 2011). *Deterministic models*, apply a fixed, single concentration value (chemical occurrence) to fixed summary statistics on food or beverage intake (food consumption). *Distributional models* apply a fixed, single concentration value for a given commodity or food category (chemical occurrence), to individual-based dietary consumption records (food consumption). *Probabilistic models* consider variability in terms of both input parameters, namely utilizing individual substance concentration values, with an assignment of a "presence probability" indicating the frequency of that value being encountered (chemical occurrence), alongside individual dietary consumption records accounting for the full range of population intakes (food consumption).

The exposure assessments conducted in 2014 were generally conservative in nature, and in most instances focused on the maximum reported use level for each beverage category, assuming that the food additive was always present (*i.e.*, assuming 100% presence probability), and as such were primarily distributional or deterministic in nature. The 2015 JECFA assessments summarized in the introduction (JECFA, 2016) are presumed to have similarly assumed 100% presence probability, whilst using average, rather than maximum use level. In our 2016 refined assessment, however, two model types were conducted for the U.S., Canada and Mexico: *Probabilistic* and *Distributional*. In Brazil, only *Deterministic* models were allowable based on the absence of individual-based food consumption data and the availability of summary statistics for food consumption data; a deterministic model was also conducted for Mexico as summary statistics for beverage consumption were likewise published for this country to complement the *probabilistic* and *distributional* assessments; however, it is noted that the assessments based on the individual data are considered more realistic. The general concepts that were incorporated into these updated intake assessments are summarized as follows:

- The 'probabilistic' models (U.S., Canada, Mexico) involved the application of a brand-specific presence probability for all reported typical use levels of benzoates (including zeros), based on brand market share, for each beverage category. This assessment model may be considered the most representative of intakes by a non-brand loyal consumer, wherein it takes into account the variability associated with benzoate usage in beverages consumed as part of the diet. Each concentration point is assigned a "presence probability" (in other words, a probability of occurrence) which can be tailored

to represent market share. Taken together, this model type also allows for the representation of a wide spectrum of benzoate use levels (including beverage brands reporting no use of benzoates and those reporting an exceedance of the adopted Codex interim 250 ppm use levels), with the probability of such beverages being consumed reflective of the market share of these brands.

- The 'brand-loyal' models (distributional - U.S., Canada and Mexico; deterministic – Brazil and Mexico) assumed consumers were brand-loyal to the highest-contributing beverage category (*i.e.*, the maximum typical use level was assigned a 100% presence probability[2]) while concentrations of benzoates for the remaining beverage categories were calculated using an average reported level, weighted by market share. To account for these specific consumers who may be habitually consuming beverages with higher benzoates due to preference and pre-established loyalty toward a specific product line, the highest reported concentration of benzoates for the largest contributing beverage sub-category was incorporated in this model, whereas the market-weighted mean concentration was utilized for the remaining beverage categories.

  This evaluation allows for the representation of all beverage brands and their reported typical benzoate use levels (across the beverage categories), but also accounts for potential brand-loyal consumers who have a tendency to consume the same beverage brand and beverage product over long periods of time.

- The 'deterministic maximum' model (Brazil) applied the interim ML level of 250 ppm to all beverage categories to determine the potential exposure based on the interim ML for beverage types for which benzoates were reported to be used.

While it is noted that the models described above are intended to render a more realistic/accurate estimate of actual benzoate intake from these beverage categories, it is noted that the assessment models have retained a suitable level of conservatism based on the following aspects:

- Although it is proposed that an ML of 250 ppm will be applied to products with a pH ≤3.5 (per the interim ML adopted by Codex), the 'probabilistic' models (U.S., Canada, Mexico) incorporated **all** reported use levels – even if these values were higher than 250 ppm. This produced intake estimates in the probabilistic models that were truly reflective of the current situation without the enforcement of the ML.

[2] In order to determine the top contributing category to total exposure, a preliminary assessment was conducted in which the interim ML was applied to all 14.1.4 categories, and the main contributing category was identified for the total population of interest.

- In a similar manner, all reported use levels (including those which are higher than 250 ppm), were utilized to establish the market weighted average level applied to the 'other' categories in the 'brand-loyal' models (U.S., Canada, Mexico and Brazil).

- The 'brand loyal' models (U.S., Canada, Mexico and Brazil) account for consumers which may be repeatedly consuming beverages with the highest reported amount of benzoate for the product category – irrespective of whether these reported values accounted for a large proportion of the market. It is noted that brand loyal consumers may equally be consuming beverages which contain a lower use level, or are benzoate free, which is the more likely scenario given the predominant market share of benzoate-free products (see individual graphs reporting the proportion of benzoate-containing beverage in the following sections for each respective jurisdiction).

- Although the market-weighted average values were weighted to consider non-occurrence in specific brands, the 'brand loyal' exposure models (U.S., Canada, Mexico and Brazil) assumed 100% presence probability for all beverage categories in which benzoates were reported to be used. The 'deterministic maximum' model (Brazil) applied a maximum level to all beverage categories.

Table 2.2-1 Summary of the Dietary Intake Assessment Models Used to Estimate Exposure to Benzoates from Non-Alcoholic Beverages (2014 and 2016 Evaluations)

Country	Assessment Year	Assessment Type	Food Consumption Data	Chemical Data	
				Concentration Values Used	Presence Probability
United States	2014	Distributional (Scenario 1)	NHANES (individual subject data)	Maximum reported level for beverage category	100%
		Probabilistic (Scenario 2)	NHANES (individual subject data)	Brand-specific maximum reported levels	Equal likelihood of any level selected
	2016	Probabilistic (Model 1)	NHANES (individual subject data)	Individual brand-specific use levels	Weighted according to market share
		Distributional Brand Loyal (Model 2)	NHANES (individual subject data)	1. Top contributing category: Maximum reported level[1] 2. Remaining categories: market-weighted average reported level	100%, with the exception of entire categories in which no benzoate use was reported.
Canada	2014	Not included			
	2016	Probabilistic (Model 1)	NHANES (surrogate consumption data)[2]	Individual brand-specific use levels	Weighted according to market share
		Distributional Brand Loyal (Model 2)	NHANES (surrogate consumption data) [2]	1. Top contributing category: Maximum reported level[1] 2. Remaining categories: market-weighted average reported level	100%, with the exception of entire categories in which no benzoate use was reported.
Mexico	2014	Distributional	ENSANUT 2012 FFQ	Maximum reported level for beverage category	100%
		Deterministic	ENSANUT 2012 24-hour recall (published values)	Maximum reported level for beverage category	100%
	2016	Deterministic Brand Loyal (Model 1)	ENSANUT 2012 24-hour recall (published values)	1. Top contributing category: Maximum reported level[3] 2. Remaining categories: market-weighted average reported level	1. Top contributing category: 100% 2. Non-occurrences within a beverage category: 0%
		Probabilistic (Model 2)	ENSANUT 2012 FFQ	Individual brand-specific use levels	Non-occurrences included in model, weighted according to market share

Table 2.2-1 Summary of the Dietary Intake Assessment Models Used to Estimate Exposure to Benzoates from Non-Alcoholic Beverages (2014 and 2016 Evaluations)

Country	Assessment Year	Assessment Type	Food Consumption Data	Chemical Data	
				Concentration Values Used	Presence Probability
		Distributional Brand Loyal (Model 3)	ENSANUT 2012 FFQ	1. Top contributing category: maximum reported level[3] 2. Remaining categories: market-weighted average reported level	1. Top contributing category: 100% 2. Non-occurrences included in model, weighted according to market share
Brazil	2014	Deterministic	Household Budget Survey (POF) 2008-2009	Maximum reported level for beverage category	100%
	2016	Deterministic Maximum	Household Budget Survey (POF) 2008-2009	Maximum reported level for categories reporting benzoate use[4]	100%, with the exception of entire categories in which no benzoate use was reported.
	2016	Deterministic Brand Loyal	Household Budget Survey (POF) 2008-2009	1. Top contributing category: maximum reported level [3] 2. Remaining categories: market-weighted average reported level	1. Top contributing category: 100% 2. Non-occurrences within a beverage category: 0%

ENSANUT = Encuesta Nacional de Salud y Nutrición; FFQ = food frequency questionnaire; NHANES = United States National Health and Nutrition Examination Survey; POF = Pesquisa de Orçamentos Familiares.
Note: Assessments included in the current report are marked in green shade.
[1] If the maximum reported level for the highest contributing beverage category exceeded 250 ppm, the value was restricted to the Codex adopted interim level of 250 ppm for beverages with a pH ≤3.5 (no such restriction was place on beverage with a pH >3.5), see individual sections for the specific values included in the models.
[2] U.S. NHANES data were used as a surrogate to represent Canadian consumption patterns. Although Statistics Canada [as part of the Canadian Community Health Survey - Nutrition (CCHS)] collates Canadian consumption patterns, these are not available for public use.
[3] If the maximum reported level reported for the highest contributing beverage category exceeded 250 ppm, the value was restricted to 250 ppm for beverages (as per the Codex adopted levels).
[4] If the maximum reported level for any beverage categories exceeded 250 ppm, the value was restricted to 250 ppm (as per the Codex adopted levels).

3.0 UNITED STATES

3.1 Food Consumption Survey Data

The current assessment of benzoate exposure was calculated using updated reported use levels collated from members of the ICBA in conjunction with food consumption data included in the U.S. National Center for Health Statistics' (NCHS) National Health and Nutrition Examination Surveys (NHANES) 2011-2012 (USDA, 2014; CDC, 2015). Calculations for the mean and 95th percentile all-person (general population) and all-user (consumers only) intakes were performed for all non-alcoholic beverage categories and the individual non-alcoholic beverage sub-categories. Results are presented on a body weight basis (mg/kg body weight/day) and as a proportion of the acceptable daily intake (% ADI) for benzoates (*i.e.*, 5 mg/kg body weight/day; JECFA, 1997) for the following population groups:

Toddlers and young children, 1 to 7 years;
Children and Adolescents, ages 8 to 17;
Adults aged 18 years and over; and
Total population (all age and gender groups combined; including infants under 1 year).

3.1.1 Survey Description

NHANES for the years 2011-2012 are available for public use and were the ones used by ICBA in its 2014 JECFA submission. To ensure consistency between the 2014 and 2016 assessments and to facilitate the comparison of the results produced from both sets of analyses, the 2011-2012 NHANES survey cycle was also used in the current 2016 assessment. NHANES are conducted as continuous, annual surveys, and are released in 2-year cycles. Each year approximately 7,000 people from 15 different locations across the U.S. are interviewed, and approximately 5,000 complete the health examination component of the survey. Any combination of consecutive years of data collection is recognized and used as a nationally representative sample of the U.S. population. Two 24-hour dietary recalls administered on 2 non-consecutive days are available from the NHANES 2011-2012 survey; these data were used to generate estimates for the current intake analysis.

NHANES 2011-2012 survey data were collected from individuals and households *via* 24-hour dietary recalls administered on 2 non-consecutive days (Day 1 and Day 2) throughout all 4 seasons of the year. Day 1 data were collected in-person, and Day 2 data were collected by telephone in the following 3 to 10 days, on different days of the week, to achieve the desired degree of statistical independence. The data were collected by first selecting Primary Sampling Units (PSUs), which were counties throughout the U.S., of which 15 PSUs are visited per year. Small counties were combined to attain a minimum population size. These PSUs were segmented and households were chosen within each segment. One or more participants within

a household were interviewed. For NHANES 2011-2012, 13,431 individuals were selected for the sample, 9,756 were interviewed (72.6%) and 9,338 were sampled (69.5%).

In addition to collecting information on the types and quantities of foods being consumed, NHANES 2011-2012 collected socio-economic, physiological and demographic information from individual participants in the survey, such as sex, age, height and weight, and other variables useful in characterizing consumption. The inclusion of this information allows for further assessment of food intake based on consumption by specific population groups of interest within the total population. The sample design for NHANES 2011-2012 includes an oversample of Asian Americans. However, sample weights were incorporated to allow estimates from these subgroups to be combined to obtain national estimates that reflect the relative proportions of these groups in the population as a whole (USDA, 2014; CDC, 2015).

3.1.2 Statistical Methods

Two exposure assessment models were employed for the assessment of intakes of benzoates in the U.S. based on the data available:

1. Probabilistic model using all 'typical' reported use levels for each beverage product having a specific likelihood of being consumed based on market share data (customized "presence probability"), combined with individual food consumption data for the U.S. population (Model 1 – 'Probabilistic assessment'). A target number of 100,000 person-days was used for the probabilistic assessment[3].

2. Distributional model using the highest 'typical' reported use level for the main contributing beverage category (identified as regular carbonated soft drinks), and a market-weighted mean of typical use levels for the remaining beverage categories, combined with individual food consumption data for the U.S. population (Model 2 – 'Brand loyal Deterministic assessment').

For both exposure assessments, consumption data from individual dietary records, detailing beverages ingested by each survey participant, were collated and used to generate estimates for the intake of benzoates by the U.S. population[4]. Estimates for the daily intake of benzoates represent projected 2-day averages for each individual from Day 1 and Day 2 of NHANES 2011-2012 data; these average amounts comprised the distribution from which mean and percentile intake estimates were generated. Mean and percentile estimates were generated incorporating

[3] In the NHANES 2011-2012 dataset, this is equivalent to approximately 7 iterations.
[4] Statistical analysis and data management were conducted in DaDiet Software (Dazult Ltd., 2016). DaDiet Software is a web-based software tool that allows accurate estimate of exposure to nutrients and to substances added to foods, including contaminants, food additives and novel ingredients. The main input components are concentration (use level) data and food consumption data. Data sets are combined in the software to provide accurate and efficient exposure assessments.

survey weights in order to provide representative intakes for the entire U.S. population. "All-person" or "general population" intake refers to the estimated intake of benzoates averaged over all individuals surveyed, regardless of whether they consumed beverage products potentially containing benzoates, and therefore includes individuals with "zero" intakes (*i.e.*, those who reported no intake of food products containing benzoates during the 2 survey days). "All-user" or "consumers only" intake refers to the estimated intake of benzoates by those individuals who reported consuming food products potentially containing benzoates, hence the "consumer only" designation. Individuals were considered 'users/ consumers' if they consumed 1 or more non-alcoholic beverages on either Day 1 or Day 2 of the survey.

Mean and 95th percentile intake estimates based on sample sizes of less than 30 and 160, respectively, may not be considered statistically reliable due to the limited sampling size (CDC, 2013). As such, the reliability of estimates for the intake of benzoates based on consumption estimates derived from individual population groups of a limited sample size may be questionable. These values are marked with an asterisk in the relevant data tables.

3.1.3 Food Consumption Data

Food codes representative of the 7 GSFA beverages categories listed in Table 3.2-1 were chosen from the NHANES 2011-2012 dataset (USDA, 2014; CDC, 2015). All food codes included in the current intake assessment are listed in Appendix B. There was no reported consumption of food category *14.1.3.4 Concentrates for Vegetable Nectars*, therefore, food codes for vegetable juices were selected to represent intakes of this food category. Product-specific adjustment factors were developed based on data provided in the standard recipe file for the Continuing Survey of Food Intakes by Individuals (CSFII) 1994-1996, 1998 survey (USDA, 2000).

3.2 Concentration Data

Benzoate use levels (on a benzoic acid basis) and brand market share data for beverage products currently available on the U.S. market were collated by the ICBA. All individual brand-specific concentrations were input into the probabilistic assessment (Model 1), whereas the market-weighted average use level and the highest reported benzoate use level for the main contributing beverage category (regular carbonated soft drinks) were utilized for the distributional intake assessment (Model 2).

Brand-specific benzoate use levels in each beverage category are trade secret and considered privileged and confidential. The market-weighted averages and highest reported concentrations of benzoate use in the beverage categories, utilized in the distributional intake assessment, are

presented in the Table 3.2-1 below. With particular respect to *maximum*[5] reported levels summarized in the right-most column, use levels in beverages of pH ≤3.5 and >3.5 were restricted as to not exceed 250 ppm (per the Codex adopted interim level for benzoates) and 500 ppm, respectively, if warranted. It was observed that no market-weighted average concentration exceeded 250 ppm, even when factoring reported benzoate use levels over 250 ppm in certain brands. Therefore, industry-reported concentrations were not altered when calculating the market-weighted average benzoate concentration.

It is further highlighted that a large proportion of the non-alcoholic beverage market had indicated no benzoate use (*i.e.*, 0 ppm), which is reflected in the market-weighted average benzoate use level but may not be readily apparent looking at the aggregated data below. The distribution of benzoate use among the non-alcoholic beverage industry is illustrated in Figure 3.2-1 below.

Table 3.2-1 Weighted Average and Maximum Reported Use Levels of Benzoate in the U.S., by Codex GSFA Food Category, as Utilized in the Exposure Assessment Models

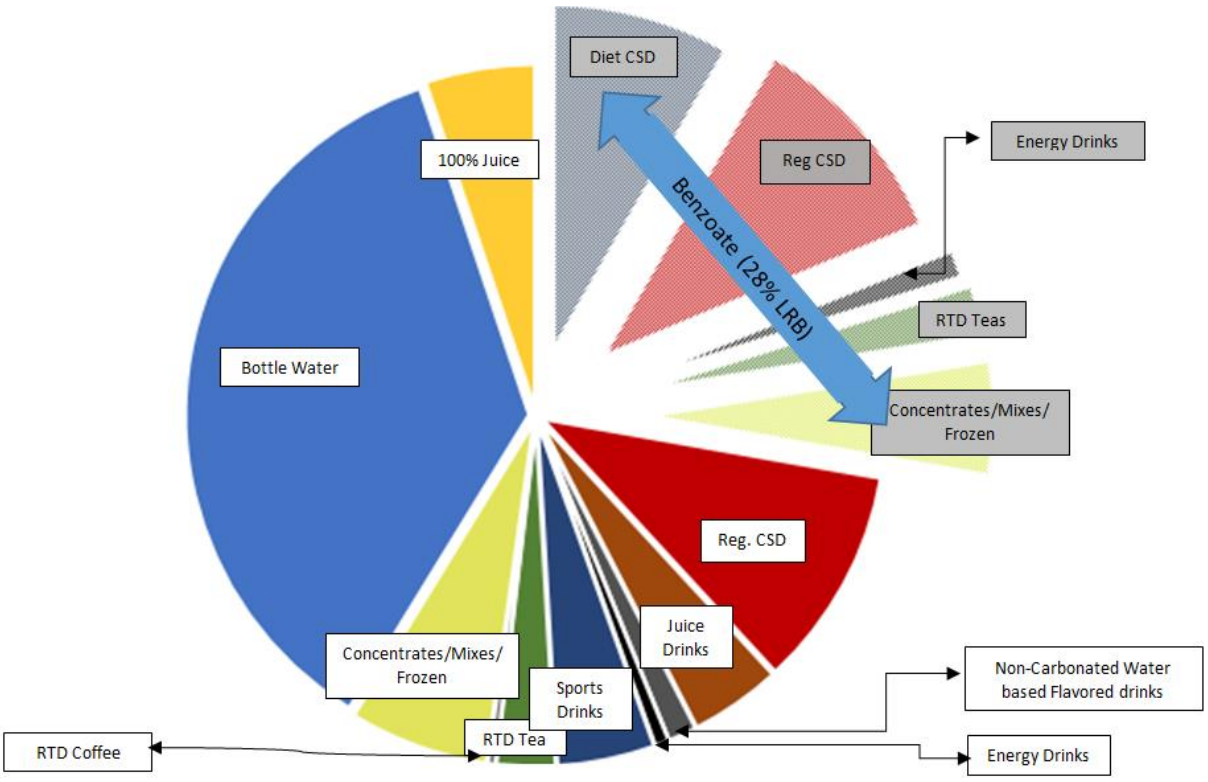
GSFA Food Category	Benzoates Use Level (ppm)	
	Market-Weighted Average Use Level	Highest Reported Typical Level
14.1.2.1 Fruit Juice	0	0
14.1.2.3 Concentrates for Fruit Juice[1]	0	0
14.1.3.1 Fruit Nectar[2]	0	0
14.1.3.3 Concentrates for Fruit Nectar[2]	0	0
14.1.3.4 Concentrates for Vegetable Nectars[2,3]	na	na
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks		
Diet Carbonated Soft Drinks	196.7	367 (pH ≤3.5) 400.0 (pH >3.5)
Regular Carbonated Soft Drinks	183.5	311[4] (pH ≤3.5) 428.3 (pH >3.5)
Energy Drinks	110.9	430.5
Flavoured Water Drinks	3.8	196.5
Fruit Juice-Based Drinks, including concentrates	0	0
Ready-to-Drink Teas	67.1	196.0
Sports Drinks	0	0

[5] Note: Values as reported by industry (including concentrations above 250 ppm) were included in the calculation of the weighted ‘average’ values (see next paragraph).

Table 3.2-1 Weighted Average and Maximum Reported Use Levels of Benzoate in the U.S., by Codex GSFA Food Category, as Utilized in the Exposure Assessment Models		
GSFA Food Category	**Benzoates Use Level (ppm)**	
	Market-Weighted Average Use Level	**Highest Reported Typical Level**
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0

GSFA = General Standard for Food Additives; na = not available; ppm = parts per million; U.S. = United States.
[1] No values were collated for the fruit juice concentrate category in 2016, therefore values obtained for '14.1.2.1 Fruit juice' were utilized based on feedback from ICBA members
[2] Concentration data collected in 2014 (not included in 2016 data collection).
[3] No data reported for this beverage category in 2014, data for other nectars were applied to this category.
[4] Values were restricted to 250 ppm for beverages of pH ≤ 3.5 based on the Codex adopted interim level, in the 'brand-loyal model' only for the main contributing category. In contrast, **all** available use levels were used in the calculation of the market-weighted average use levels in this mode, and in the probabilistic model.

Figure 3.2-1 Distribution of Benzoate Use Among the Liquid Refreshment Beverage Sector in the United States



3.3 Food Survey Results

Estimates for the total mean and heavy-level (95th percentile) daily intake of benzoates from non-alcoholic beverages, using a probabilistic model and a brand-loyal model, are presented in Sections 3.3.1 and 3.3.2, respectively. Results are presented on a *per kilogram body weight* basis (mg/kg body weight/day), and expressed as a proportion of the ADI (% ADI) for the general population and consumers-only. Results for the estimated intake of benzoates from each individual beverage sub-category in each age bracket are included as supplementary data in Appendix A.

3.3.1 Model 1 - Probabilistic Assessment

Table 3.3.1-1 summarizes the estimated total intake of benzoates (mg/kg body weight/day; % ADI) from all non-alcoholic beverages permitted to contain benzoates in the U.S. determined using the probabilistic model.

The total mean and 95th percentile intakes among all ages were 0.5 and 2.2 mg/kg body weight/day (10.3 and 44.2% ADI), respectively, when the general population was examined; and 0.5 and 2.3 mg/kg body weight/day (10.7 and 45.6% ADI), respectively, for consumers only. The general population and consumer only intakes were similar among all age groups, ranging between 0.4 to 0.6 mg/kg body weight/day (7.1 to 11.3% ADI) at the mean and 2.0 to 2.3 mg/kg body weight/day (39.9 and 46.9% ADI) at the 95th percentile.

The results presented in Appendix A.1 demonstrate that even when exposure levels are examined by individual age groups and for specific beverage types, the ADI was not exceeded by any population group.

Table 3.3.1-1 Summary of the Estimated Exposure to Benzoates from Non-Alcoholic Beverages in the U.S. by Population Group (2011-2012 NHANES Data) - Probabilistic Model

Population Group	Age Group (Years)	Number of individuals surveyed[1]	General Population Exposure (mg/kg bw/day)		Consumer Only Exposure (mg/kg bw/day)	
			Mean (% ADI)	95th Percentile (% ADI)	Mean (% ADI)	95th Percentile (% ADI)

Table 3.3.1-1 Summary of the Estimated Exposure to Benzoates from Non-Alcoholic Beverages in the U.S. by Population Group (2011-2012 NHANES Data) - Probabilistic Model						
Toddlers and Young Children	1 to 7	1,241	0.4 (7.1)	2.1 (42.1)	0.4 (7.7)	2.1 (42.6)
Other Children, Including Adolescents	8 to 17	1,468	0.4 (9.0)	2.0 (39.9)	0.5 (9.3)	2.0 (40.1)
Adults	18 and Older	4,506	0.6 (11.0)	2.3 (46.0)	0.6 (11.3)	2.3 (46.9)
Total Population	All Ages	7,546	0.5 (10.3)	2.2 (44.2)	0.5 (10.7)	2.3 (45.6)

ADI = acceptable daily intake; bw = body weight; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
[1] The probabilistic assessment was conducted using a target of 100,000 person-days; equivalent to approximately 7 iterations of NHANES.
Note: % ADI expressed as a percentage of 5 mg/kg bw/day, the group ADI expressed as benzoic acid which was assigned at the forty-sixth meeting of the CCFA (JECFA, 1997).

3.3.2 Model 2 - Brand-Loyal Distributional Assessment

Table 3.3.2-1 summarizes the estimated total intake of benzoates (mg/kg body weight/day; % ADI) from all non-alcoholic beverages in the U.S. population, assuming the "regular carbonated soft drink" category contained the maximum level of benzoate use [428.3 ppm (for beverages with a pH >3.5, represented by cream sodas and root beers) or 250 ppm (all other regular carbonated soft drinks) per the Codex adopted interim level] with a weighted mean value utilized for all other beverage categories (see Table 3.2-1).

In the general population, estimates of the mean and 95th percentile benzoate intakes were 0.9 and 3.3 mg/kg body weight/day, respectively, among all ages (representing 17.3 and 65.6% of ADI, respectively). The mean and 95th percentile intakes of benzoates were 0.9 and 3.4 mg/kg body weight/day (18.1 and 67.6% ADI), respectively, among consumers-only. As with Model 1, mean brand loyal (Model 2) consumer only intakes were similar among all population groups but were higher than those determined using the probabilistic approach. Toddlers and young children (1 to 7 years) were identified as having the highest 95th percentile all-user intakes of any age group of 4.1 mg/kg body weight/day (82.4% ADI), whereas other children, including adolescents, and adults had similar 95th percentile all-user intakes ranging between 3.2 to 3.5 mg/kg body weight/day (64.2 to 70.6% ADI).

When these results were dissected further, to investigate exposure by individual age groups for each specific type of beverage (as described in Appendix A.2), the subset of toddlers and young children (ages 1 to 7) that were identified to be consumers of regular carbonated soft drinks, only, were observed to exceed the ADI at the 95th percentile (5.36 mg/kg body weight/day; Table A.2-1). The exceedance was minor (7.2% ADI) but in the interest of further investigating potential subpopulations that may exceed the ADI, this subpopulation of toddlers and young

children was isolated. When examining toddlers and children that were specifically estimated to have benzoate intakes greater than 5.0 mg/kg body weight/day on an individual level, this was determined to be represented by 18 toddlers/young children out of a survey comprising of 1,241 toddlers and young children (*i.e.*, 1.5%) and of 7,546 total (all ages) U.S. respondents (*i.e.*, 0.2%). These particular toddlers/children – only 1.5% of toddlers/children surveyed – slightly exceed the ADI when they are assumed to habitually consume regular carbonated soft drinks at the maximum benzoate use level of 428.3 ppm (for cream sodas and root beers) or 250 ppm for all other regular carbonated soft drinks. In the overall context of the total NHANES survey, the exceedance by such a small proportion of the population (*i.e.*, 0.2%) does not serve as an appropriate basis for risk assessment and risk management decisions. Therefore, the overall estimated 95th percentile of consumption among toddlers and young children, of 4.1 mg/kg body weight/day (Table 3.3.2-1 below), is considered the more relevant figure and is more representative of "usual" intakes by this young population group.

Table 3.3.2-1 Summary of the Estimated Exposure to Benzoates from Non-Alcoholic Beverages in the U.S. by Population Group (2011-2012 NHANES Data) - Brand Loyal Model

Population Group	Age Group (Years)	Number of individuals surveyed	General Population Exposure (mg/kg bw/day)		Consumer Only Exposure (mg/kg bw/day)	
			Mean (% ADI)	95th Percentile (% ADI)	Mean (% ADI)	95th Percentile (% ADI)
Toddlers and Young Children	1 to 7	1,241	0.7 (14.9)	4.0 (80.8)	0.8 (16.1)	4.1 (82.4)
Other Children, Including Adolescents	8 to 17	1,468	0.9 (19.0)	3.5 (70.6)	1.0 (19.7)	3.5 (70.6)
Adults	18 and Older	4,506	0.9 (17.6)	3.2 (63.8)	0.9 (18.1)	3.2 (64.2)
Total Population	All Ages	7,546	0.9 (17.3)	3.3 (65.6)	0.9 (18.1)	3.4 (67.6)

ADI = acceptable daily intake; bw = body weight; NHANES = National Health and Nutrition Examination Survey; U.S. = United States

3.3.3 Percent Consumers of Individual Beverage Categories

Estimates for the mean and 95th percentile daily intakes of benzoates from each individual non-alcoholic beverage category are summarized in the tables included in Appendix A, for both the probabilistic and the brand-loyal distributional models. The total U.S. population (*i.e.*, all ages) was identified as being significant consumers of regular carbonated soft drinks (40.7%), fruit juice-based drinks (18.3%) and diet carbonated soft drinks (17.7%). As mentioned in Section 2.2., the brand loyal model applied the highest reported use levels for regular carbonated soft drinks [428 ppm (beverages with pH >3.5, represented by cream sodas and root beers) and 250 ppm (remaining regular soft drink types) per the Codex adopted interim level] to all consumption events of these beverages, whilst applying the market-weighted

average level to all other beverage types. When the percent consumers of regular carbonated soft drinks was investigated according to individual population groups (recall that an individual is considered a consumer of the beverage in question if it was consumed at least once on either of the 2 survey days), adolescents were identified to have the highest percent consumers of regular carbonated soft drinks, at 55.8%, followed by adults at 39.5%. Toddlers and young children had the lowest percent consumers, at 33.8%.

3.3.4 Contribution of Individual Beverage Categories to Total Mean Intakes

As benzoate use was reported to be "0" in GSFA categories 14.1.2, 14.1.3, and 14.1.5 - *i.e.*, juices, nectars, coffee/tea, respectively - no sources of benzoate exposure was modelled from beverages belonging to these categories (*i.e.*, all intakes originated from the consumption of products classified under GSFA category 14.1.4). Within the arbitrary subcategories of 14.1.4, regular carbonated soft drinks contributed 59.1% to overall total mean benzoate intakes in the probabilistic intake model (0.5 mg/kg body weight/day as presented in Table 3.3.1-1; Model 1) and to 75.8% of total mean intakes in the brand loyal distributional model (0.9 mg/kg body weight/day as presented in Table 3.3.2-1; Model 2) among all ages. Within toddlers and young children, specifically being identified as potentially having higher intakes than the rest of the population groups examined, regular carbonated soft drinks accounted for 83.1% of total mean benzoate intakes by this population group in the probabilistic intake model (0.4 mg/kg body weight/day, see Table 3.3.1-1) and to 94.1% of total mean intakes in the brand loyal distributional model (0.7 mg/kg body weight/day, see Table 3.3.2-1).

3.4 Conclusions for U.S. Intakes

The current exposure assessments have evaluated the intakes of benzoates from non-alcoholic beverages among the U.S. population based on individual food consumption data from the NHANES 2011-2012. Intake data are presented in terms of general population and consumers only for individual age groups and for the total U.S. population on a bodyweight basis, and as a percentage of the ADI (5 mg/kg body weight/day; JECFA, 1997). Two models were developed for investigating benzoate intakes: the first was a probabilistic model, taking into consideration all individual brand-specific concentration levels submitted by ICBA members and brand market share data for the U.S.; the second was a conservative "brand-loyal" model which considered specific consumers who may habitually consume the same benzoate-containing beverage which is assumed to contain benzoates at the maximum reported use level of all data submitted for the U.S. market (capped at 250 ppm for beverages pH ≤3.5 per the Codex adopted interim level for benzoates and set at 428 ppm – the highest reported use level – for beverages pH >3.5).

The first model is expected to provide realistic estimates of mean and heavy-level intakes of the additive by non-brand loyal consumers, as brands having a larger proportion of market share

are incorporated into the model with a presence probability directly reflecting the market share. The second model estimated the intakes for brand-loyal consumers, under the hypothetical scenario that they are consuming regular carbonated soft drinks containing the highest amount of benzoates reported (428 ppm in beverages with a pH >3.5 based on the highest reported use level; and 250 ppm in all other regular carbonated soft drinks based on the Codex adopted interim level for benzoates), while also consuming other non-alcoholic beverage categories, which contain benzoates at a market-weighted average level.

In summary, when each individual concentration value and market share data were incorporated into a probabilistic exposure assessment (Model 1), the mean and 95th percentile intakes of the total population were calculated to be 0.5 and 2.2 mg/kg body weight/day (10.3 and 44.2% ADI), respectively. In consumers only, the mean and 95th percentile intakes among all ages were 0.5 and 2.3 mg/kg body weight/day (10.7 and 45.6% ADI), respectively. Total benzoate intake did not exceed the ADI in any age bracket examined (see Appendix A.1).

With regard to Model 2 (brand-loyal), the total population intakes were 0.9 and 3.3 mg/kg body weight/day at the mean and 95th percentile (17.3 and 65.6% ADI), respectively, when the general population was considered (*i.e.*, including individuals who did not consume non-alcoholic beverages). Among consumers only, the mean and 95th percentile intakes were 0.9 and 3.4 mg/kg body weight/day (18.1 and 67.6% ADI), respectively, for all ages combined. Toddlers and young children were identified to have the highest heavy-level exposure (*i.e.,* at the 95th percentile) when all beverage types were considered, at 4.1 mg/kg body weight/day (82.4% ADI).

4.0 CANADA

4.1 Food Consumption Survey Data

National consumption data are collated by Statistics Canada as part of the Canadian Community Health Survey - Nutrition (CCHS). However, this information is not released to the public and therefore was not available for the current intake assessment. Given the relative similarity between U.S. and Canadian diets, the U.S. NHANES food consumption data[6] were used as a surrogate to examine exposure to benzoates by this population group.

As such, the same probabilistic and brand-loyal models described in Section 3.1 for the U.S. market above were applied for the Canadian assessment here; however, Canada-specific benzoate concentration values and beverage market share data were incorporated.

[6] See Section 3.1.1 for the complete survey description for the NHANES 2011-2012 dataset.

4.2 Concentration Data

As with the previously described assessments, benzoate use levels (on a benzoic acid basis) and market share data for the Canadian market were collated by the ICBA. Individual brand-specific concentrations and market share data were input into the probabilistic assessment (Model 1) whereas the market-weighted average use level and the highest reported use level for the highest contributor, regular carbonated soft drinks[7], were used in the brand-loyal distributional intake assessment (Model 2). As with the U.S. assessments, brand-specific benzoate use levels and market share data were collected by the ICBA and are considered privileged and confidential. The market-weighted averages and highest reported concentration of benzoate use in the GSFA beverage categories, utilized in the brand-loyal distributional intake assessment, are presented in the table below. Specifically for the highest contributing category, regular carbonated soft drinks, instances in which the maximum reported use levels exceeded 250 ppm (in beverages of pH ≤3.5), the maximum level was restricted to 250 ppm based on the Codex adopted interim level (no such restriction was applied to beverages with a pH >3.5 as no reported levels exceeded 500 ppm). For the other beverage types, similar restrictions were not applied and no market-weighted average benzoate concentration values exceeded these limits. The proportion of benzoate-containing non-alcoholic beverages on the Canadian market is illustrated in Figure 4.2-1 below.

[7] Regular carbonated soft drinks were further divided into beverages expected to contain a pH >3.5 (cream sodas and root beers), and all other regular carbonated soft drinks (having a typical pH of ≤3.5). In the brand-loyal distributional model, the maximum limit of 250 ppm was applied to regular carbonated soft drinks with pH ≤3.5 whereas the highest reported level of 438 ppm was applied to regular carbonated soft drinks with pH>3.5.

Table 4.2-1 Weighted Average and Maximum Reported Use Levels of Benzoate in Canada, by Codex GSFA Food Category

GSFA Food Category	Benzoates Use Level (ppm)	
	Market-Weighted Average Use Level	Highest Reported Typical Level
14.1.2.1 Fruit Juice	0	0
14.1.2.3 Concentrates for Fruit Juice[1]	na	na
14.1.3.1 Fruit Nectar[2]	na	na
14.1.3.3 Concentrates for Fruit Nectar[2]	na	na
14.1.3.4 Concentrates for Vegetable Nectars[2, 3]	na	na
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks		
Diet Carbonated Soft Drinks	167.3	235 (pH ≤ 3.5) 690 (pH > 3.5)
Regular Carbonated Soft Drinks	71.3	250[4] (pH ≤ 3.5) 438 (pH > 3.5)
Energy Drinks	108.5	250*
Flavoured Water Drinks	0	0
Fruit Juice-Based Drinks, including concentrates	0	0
Ready-to-Drink Teas	55.6	91.1
Sports Drinks	0	0
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa[2]	0	0

GSFA = General Standard for Food Additives; na = not available; ppm = parts per million.

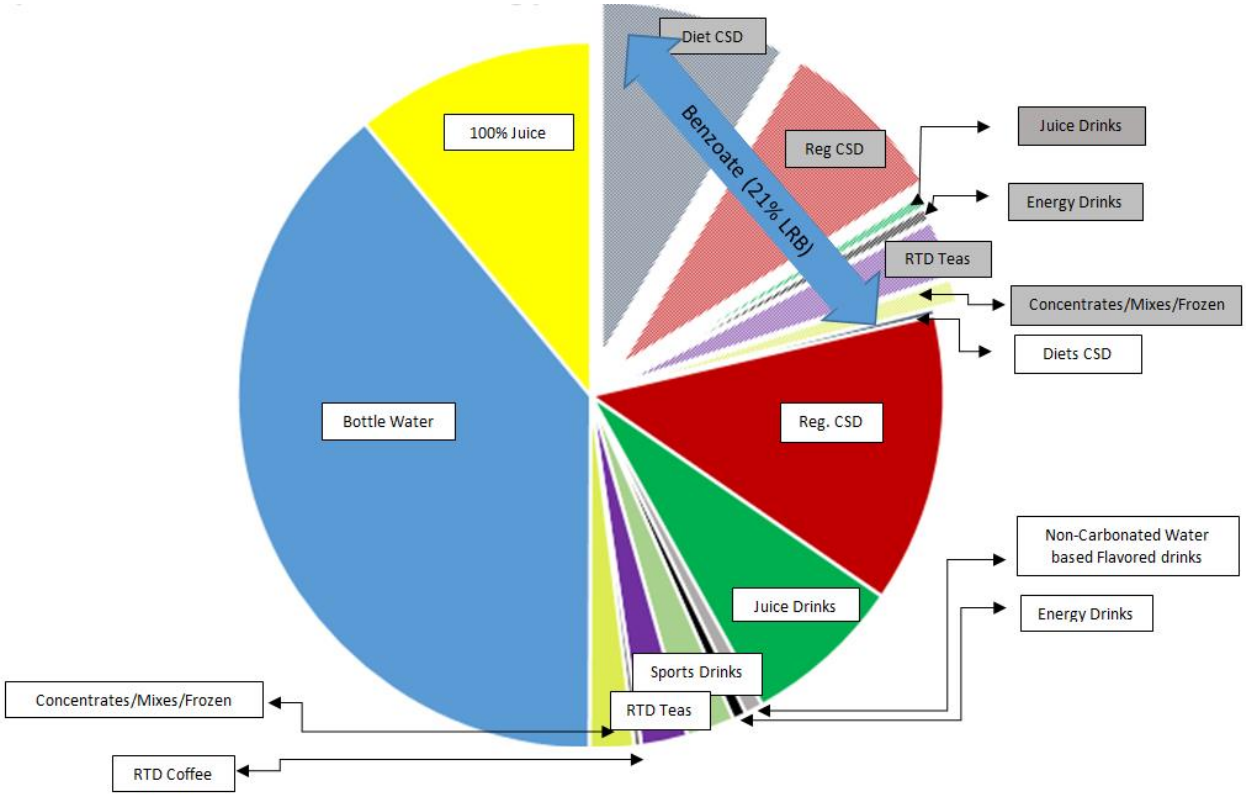
[1] No values obtained for the fruit juice concentrates category, therefore values obtained for '14.1.2.1 Fruit juice' were utilized based on feedback from ICBA members.

[2] The 2014 U.S. use level data were utilized for the fruit nectar categories here (as the latter were not included in the 2016 data collection effort).

[3] No data reported for the vegetable nectar category in the U.S. in 2014, thus data for other nectars were applied to this category.

[4] Values were restricted to 250 ppm for beverages of pH ≤ 3.5 based on the Codex adopted interim level, in the 'brand-loyal model' only for the main contributing category. In contrast, **all** available use levels were used in the calculation of the market-weighted average use levels in this mode, and in the probabilistic model.

Figure 4.2-1 Distribution of Benzoate Use Among the Liquid Refreshment Beverage Sector in Canada



4.3 Food Survey Results

Estimates for the total mean and heavy-level (95th percentile) intakes of benzoates from non-alcoholic beverages, using the probabilistic and brand-loyal models, are presented in Sections 4.3.1 and 4.3.2, respectively. As indicated in Section 4.1, the estimated intakes for the Canadian population were calculated using U.S. food consumption data (NHANES) as a surrogate dataset, combined with benzoate usage data specific to Canada. Results are presented on a *per kilogram body weight* basis (mg/kg body weight/day), and expressed as a percentage of the ADI (% ADI) for the general population and consumers-only. Results for the estimated intake of benzoates from each food sub-category for each age bracket are included as supplementary data in Appendix C.

4.3.1 Model 1 - Probabilistic Assessment

Table 4.3.1-1 summarizes the estimated total intake of benzoates (mg/kg body weight/day; % ADI) from non-alcoholic beverages in Canada.

The mean and 95th percentile intakes by the total population (all ages) were 0.4 and 1.7 mg/kg body weight/day, respectively, for both the general population and when consumers only were examined (equivalent to 7.4 to 7.7% and 34.5 to 35.0% ADI, respectively). Results were similar among the individual age groups, with mean results ranging from 0.2 to 0.4 mg/kg body weight/day (4.5 to 8.3% ADI), and 95th percentile values ranging from 1.6 to 1.8 mg/kg body weight/day (32.5 to 36.2% ADI).

The results presented in Appendix C.1 demonstrate that even when exposure levels are examined by individual age groups and for specific beverage types, the ADI was not exceeded by any population group.

Table 4.3.1-1 Summary of the Estimated Exposure to Benzoates from Reported Use Levels in Beverages in the Canadian Population Group (2011-2012 NHANES Surrogate Data) - Probabilistic Model

Population Group	Age Group (Years)	Number of Individuals Surveyed[1]	General Population Exposure (mg/kg bw/day)		Consumer Only Exposure (mg/kg bw/day)	
			Mean (% ADI)	95th Percentile (% ADI)	Mean (% ADI)	95th Percentile (% ADI)
Toddlers and Young Children	1 to 7	1,241	0.2 (4.5)	1.6 (32.5)	0.2 (4.9)	1.6 (32.5)
Other Children, Including Adolescents	8 to 17	1,468	0.3 (6.5)	1.7 (33.6)	0.3 (6.7)	1.8 (35.4)
Adults	18 and Older	4,506	0.4 (8.1)	1.7 (35.0)	0.4 (8.3)	1.8 (36.2)
Total Population	All Ages	7,546	0.4 (7.4)	1.7 (34.5)	0.4 (7.7)	1.7 (35.0)

ADI = acceptable daily intake; bw = body weight; NHANES = United States National Health and Nutrition Examination Survey.
[1] The probabilistic assessment was conducted using a target of 100,000 person-days; equivalent to approximately 7 iterations of NHANES.
Note: % ADI expressed as a percentage of 5 mg/kg bw/day, the group ADI expressed as benzoic acid which was assigned at the forty-sixth meeting of the CCFA (JECFA, 1997).

4.3.2 Model 2 - Brand Loyal Distributional Assessment

Table 4.3.2-1 summarizes the estimated total intake of benzoates (mg/kg body weight/day; % ADI) from all non-alcoholic beverages in the Canadian population, assuming that Canadians are brand-loyal consumers of regular carbonated soft drinks containing the highest concentrations of benzoates (438 ppm for beverages with a pH >3.5 according to the highest reported level and 250 ppm for other regular carbonated soft drinks based on the Codex adopted interim limit), utilizing the market-weighted average for all other categories.

On a body weight basis, the mean and 95th percentile of intakes of benzoates by the general population of all ages were 0.8 and 3.2 mg/kg body weight/day (16.8 and 64.4% ADI),

respectively. Among consumers-only, the mean and 95th percentile of intakes for all ages were 0.9 and 3.4 mg/kg body weight/day (17.6 and 67.2% ADI), respectively. In general, the estimated mean intake of benzoates across the age groups examined was approximately 1 mg/kg body weight/day. The highest 95th percentile intake estimate was identified in toddlers and young children of 4.1 mg/kg body weight/day (82.8% of the ADI). Among this population group (aged 1 to 7 years), 33.8% of individuals reported consumption of a regular carbonated soft drink at least once over the 2 survey days (see Section 4.3.3).

When these estimates were investigated further - to examine exposure from each specific subcategory of beverage (as described in Appendix C.2) - those toddlers and young children (ages 1 to 7) identified as heavy consumers of regular carbonated soft drinks specifically (the brand-loyal category) were observed to have 95th percentiles of benzoate intakes of 5.36 mg/kg body weight/day (107% ADI; Table C.2-1)[8]. As previously indicated for the U.S. (Section 3.3.2), the actual number of individuals expected to exceed the ADI using this model is quite low, at only 19 toddlers and children of the 1,241 toddlers and young children surveyed (*i.e.*, 1.5%) and of the total 7,546 participants of NHANES (*i.e.*, 0.2%). It is not appropriate to use these estimates corresponding to a small proportion of the population for risk assessment and risk management decisions. The overall 95th percentile estimate for this age category, of 4.1 mg/kg body weight/day, would be the most relevant estimate.

Table 4.3.2-1 Summary of the Estimated Exposure to Benzoates from Range of Reported Use Levels in Beverages in the Canadian Population Group (2011-2012 NHANES Surrogate Data) - Brand Loyal Distributional Model

Population Group	Age Group (Years)	Number of Individuals Surveyed	General Population Exposure (mg/kg bw/day)		Consumer Only Exposure (mg/kg bw/day)	
			Mean (% ADI)	95th Percentile (% ADI)	Mean (% ADI)	95th Percentile (% ADI)
Toddlers and Young Children	1 to 7	1,241	0.7 (14.6)	4.0 (80.8)	0.8 (15.8)	4.1 (82.8)
Other Children, Including Adolescents	8 to 17	1,468	0.9 (18.8)	3.6 (72.2)	1.0 (19.5)	3.6 (72.2)
Adults	18 and Older	4,506	0.9 (17.0)	3.1 (62.0)	0.9 (17.5)	3.1 (62.8)
Total Population	All Ages	7,546	0.8 (16.8)	3.2 (64.4)	0.9 (17.6)	3.4 (67.2)

ADI = acceptable daily intake; bw = body weight; NHANES = United States National Health and Nutrition Examination Survey.
Note: % ADI expressed as a percentage of 5 mg/kg bw/day, the group ADI expressed as benzoic acid which was assigned at the forty-sixth meeting of the CCFA (JECFA, 1997).

[8] Exposure levels for all other population groups, even when focusing on individual beverage types, did not exceed the ADI (see Tables C.2.1 to C.2.3).

4.3.3 Percent Consumers of Individual Beverage Categories

Estimates for the mean and 95th percentile daily intakes of benzoates from each individual non-alcoholic beverage category are summarized in the tables included in Appendix C for both the probabilistic model and the brand-loyal distributional model. Based on the use of the NHANES 2011-2012 dataset to represent food consumption patterns anticipated in the Canadian population, the proportion of consumers was the same as those reported in Section 3.3.3 for the U.S.: 40.7% of all surveyed individuals[9] reported consumption of regular carbonated soft drinks, followed by fruit juice-based drinks (18.3%) and diet carbonated soft drinks (17.7%).

4.3.4 Contribution of Individual Beverage Categories to Total Mean Intakes

In a similar manner to the U.S. assessment, the exposure to benzoates is based entirely on water-based flavored drinks (GSFA category 14.1.4) due to benzoate reported use patterns (*i.e.*, a reported use of "0" in juices – and as applied to nectars - and in coffee drinks). Regular soft drinks contributed 50.4% to overall total mean benzoate intakes in the probabilistic intake model (0.4 mg/kg body weight/day as presented in Table 4.3.1-1; Model 1) and to 78.3% of total mean intakes in the brand loyal distributional model (0.8 mg/kg body weight/day as presented in Table 4.3.2-1; Model 2) among all ages. Within toddlers and young children, specifically being identified as potentially having higher intakes than the rest of the population groups examined, regular carbonated soft drinks accounted for 86.7% of total benzoate intakes in the probabilistic intake model (0.2 mg/kg body weight/day; Table 4.3.1-1) and to 95.8% of total mean benzoate intakes in the brand loyal distributional model (0.7 mg/kg body weight/day; Table 4.3.2-1).

4.4 Conclusions for Canadian Intakes

The Canadian benzoate exposure assessment utilized country-specific benzoate concentration use level information and branded beverage market-share data; however, due to a lack of publicly available Canadian food consumption data, the United States NHANES 2011-2012 food consumption data were used as a surrogate and may anecdotally be an additional layer of conservatism added to the Canadian model. As with the intake assessment described in Section 3.0, two models were employed. The first model was a probabilistic assessment, taking into consideration all individual brand-specific concentrations reported and the market share of those brands. The second model was a "brand-loyal" scenario in which it was assumed that consumers may be habitually consuming a specific benzoate-containing beverage which has a high reported use level of benzoates. As noted in Section 2.2, the regular carbonated soft drink category was selected as the brand-loyal category based on the contribution of these products to total beverage intakes (mL/day) among the total population; however, it is noted that

[9] Adolescents reported the highest percent consumers of regular carbonated soft drinks (55.8%), followed by adults (39.5%) and toddlers and young children (33.8%).

beverages containing the maximum benzoate concentration incorporated into this model does not necessarily make up a large proportion of the market share.

In the first probabilistic model, the mean and 95th percentile intakes of the general population and consumers only were calculated at 0.4 and 1.7 mg/kg body weight/day (7.4 to 7.7% ADI and 34.5 to 35.0% ADI), respectively. The probabilistic model predicted that no age groups would exceed the ADI when concentrations of benzoates in beverages were incorporated at presence probabilities directly reflecting the market share. In the second, conservative brand-loyal model, the mean and 95th percentile of benzoate intakes among the general population were estimated to be 0.8 and 3.2 mg/kg body weight/day (16.8 and 64.4% ADI), respectively. Among consumers-only, the mean and 95th percentile was 0.9 and 3.4 mg/kg body weight/day (17.6 and 67.2% ADI), respectively, when all age groups were considered.

As with the U.S. assessment conducted with NHANES, the 2-day average benzoate intake estimates generated in this study were considered to represent suitably conservative estimates of actual long-term benzoate intakes within upper percentile groups, especially in the case of the estimates rendered in the brand-loyal model in which exposures from regular carbonated soft drinks were incorporated at the maximum use level (for which a large proportion of the market share was reported to not contain benzoates).

5.0 MEXICO

Estimates of benzoate exposure were calculated using reported use-levels collated from ICBA members in conjunction with food consumption data from the most recent Instituto Nacional de Salud Pública (INSP) Encuesta Nacional de Salud y Nutrición 2012 (ENSANUT) (INSP, 2012a). This survey gathered dietary consumption data using two different methods – a 24-hour recall and a semi-quantitative food frequency questionnaire (FFQ). Both of these data sources have been utilized to determine benzoate exposure by the Mexican population.

Initially, calculations for mean and 95th percentile benzoate intakes were determined using food consumption data collated *via* the FFQ obtained from INSP. The results are presented on a per person and per kilogram body weight basis for the following population groups:

Toddlers and young children, 1 to 7 years;
Children and Adolescents, ages 8 to 17;
Adults aged 18 years and over; and
Total population (all age and gender groups combined).

The original food consumption data collected using the 24-hour recall method was not publicly available, therefore information from the published literature regarding caloric beverages was

additionally used to calculate benzoate intakes for children (aged 1 to 19 years) and adults (aged 20 years and older)[10] (Stern *et al*., 2014).

5.1 Food Consumption Survey Data

ENSANUT 2012 is the fourth cross-sectional survey conducted by the INSP since 1988. Field work was conducted between October 2011 and May 2012. This was a nationally representative, probabilistic household survey, with a multistage stratified sample design, representative of urban rural strata and all states (Romero-Martinez *et al.,* 2013). There was an over-representation of lower socioeconomic status households in order to increase the accuracy of the estimates for this group. The sampling frame was constructed using information from the Census of Population and Housing 2005, supplemented by a list of newly created locations identified by the National Census of Population and Housing 2010. The aim of the survey was to characterize the health and nutritional status of the Mexican population (INSP, 2012b).

The survey incorporated 50,528 households (response rate of 87%), in which 96,031 individual questionnaires were applied in different age groups. These individual surveys contained a range of information regarding health and nutritional parameters. In addition, dietary information was obtained for a subsample of the population using 2 sources - a semi-quantitative food frequency questionnaire (11% of the population; 1 in 6 subjects by population group), and a 24-hour recall (13% of the population). Diet information gathered using the food frequency questionnaire utilized a validated questionnaire, consisting of a closed list of foods for which the number of days consumed per week, number of times per day, portion size, number of portions consumed during the 7 days prior to the interview was recorded for each item on the survey. The questionnaire was answered by the parent or caregiver of young children (Mundo-Rosas *et al.,* 2014).

In order to generate intake estimates from the FFQ, the data reported on the questionnaires was employed to generate an average daily intake of each of the beverages. The number of portions consumed daily was averaged according to the number of days/week the subject reported consuming a particular food; this permits an assessment of the “usual” intake of foods/beverages over a relatively long period of time (Kroes *et al*., 2002). To generate the daily intake in mL, the average daily portion size was multiplied by the benchmark established within the FFQ of 120 mL for young children and 240 mL for older children, teenagers, and adults. The food consumption data were then merged with the available demographic and anthropometric data in order to generate estimates for individual age and gender groups on a per person and a per kilogram body weight basis.

[10] Age categories were fixed according to brackets established by the study authors. As such, subpopulation groups could not be matched to JECFA age brackets as with the FFQ data.

In addition to the FFQ included in the ENSANUT survey, a single 24-hour diet recall questionnaire was administered to a subpopulation of the respondents. These data are not publicly available for use; however data on beverage intakes as measured by this questionnaire has been reported in the scientific literature (Stern *et al*., 2014). These data are employed to generate an estimate of the acute per capita intakes for children (defined as individuals aged 1 to 19 years) and adults (defined as individuals 20 years of age and older).

5.1.1 24-Hour Recall

The summary statistics on beverage consumption published by Stern *et al*. (2014) were categorized on a *per capita* (general population) and per consumer (consumers only) basis for various non-alcoholic beverage groups. Each of the beverage categories reported in this paper were matched with the GSFA beverage categorization in order to select the most appropriate concentration level to apply to intake estimates. All beverages except for plain water, milk and milk beverages, and alcoholic beverages were included in the estimation of intakes.

5.1.2 Food Frequency Questionnaire Data

Food codes representative of the 7 GSFA beverages categories were selected from the ENSANUT 2012 FFQ dataset (INSP, 2012a). All food codes included in the current intake assessment are listed in Appendix E. No food codes corresponding to energy drinks were identified; however, it is noted that benzoate use has been reported in this sector. Due to the nature of the available food codes in the ENSANUT FFQ, food codes representative of fruit and vegetable juices, concentrates, and nectars were merged. Furthermore, no codes representative of vegetable juices or concentrates were identified.

5.1.3 Statistical Methods

Three exposure assessment models were employed for the assessment of benzoate intakes in Mexico based on the two sources of consumption data available for ENSANUT:

1. Brand-loyal deterministic exposure assessment with 24-hour recall data: Summary statistics regarding beverage consumption from the 24-hour recall component of ENSANUT was used in combination with the highest reported ‘typical’ use level for the main contributing category (regular carbonated soft drinks – a 250 ppm cap per the Codex adopted interim ML for beverages with pH≤3.5) and the market-weighted average benzoate concentration for the remaining beverage types. As data are not available on an individual basis, only a deterministic evaluation is possible (Model 1 - Brand Loyal Deterministic 24-hour recall).

2. Probabilistic exposure assessment with FFQ data: all brand-specific ‘typical’ benzoate concentrations were applied with specific likelihood of being consumed based on market

share data to individual food consumption data for the Mexican population from the FFQ (Model 2 - Probabilistic FFQ Assessment).

3. Brand-loyal distributional exposure assessment with FFQ data: The highest reported 'typical' use level for the main contributing category (regular carbonated soft drinks – a 250 ppm cap per the Codex adopted interim levels for beverages with pH≤3.5[11]) and the market-weighted average benzoate concentration for the remaining beverage types was applied to individual food consumption data for the Mexican population (Model 3 - Brand Loyal Distributional FFQ Assessment).

5.2 Concentration Data

Country-specific benzoate use levels (on a benzoic acid basis) and branded beverage market data for the beverage categories of interest were collated by the ICBA. All individual brand-specific benzoate use level concentrations were input into the probabilistic assessment (Model 2), whereas the market-weighted average use level and highest reported benzoate use level for the main contributing beverage category (regular carbonated soft drinks – a 250 ppm cap per the Codex adopted interim levels for beverages with pH≤3.5[12]) were utilized for the deterministic assessment (Model 1) and the distributional brand-loyal intake assessment (Model 3).

As with other jurisdictions, a large proportion of non-alcoholic beverages were reported not to contain benzoates (see Figure 5.2-1).

[11] Due to the limited food codes available in ENSANUT, only one code for "regular soda" was identified. As such, the adopted interim ML of 250 ppm benzoates was applied to this single code. No use levels exceeding 250 ppm in regular carbonated soft drinks of pH >3.5 were reported for this jurisdiction.
[12] No benzoate use levels exceeding 250 ppm were reported for beverages of pH >3.5 in the regular carbonated soft drink category.

Table 5.2-1 Weighted Average and Maximum Reported Use Levels of Benzoate in Mexico, by Codex GSFA Food Category		
GSFA Food Category	**Benzoate Use Level (ppm)**	
	Market-Weighted Average Use Level	**Highest Reported Typical Level**
14.1.2.1 Fruit Juice	0	0
14.1.2.3 Concentrates for Fruit Juice[1]	Na	na
14.1.3.1 Fruit Nectar[2]	0	0
14.1.3.3 Concentrates for Fruit Nectar[3]	Na	na
14.1.3.4 Concentrates for Vegetable Nectars[2]	0	0
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks		
Diet Soft Drinks	168.2	299
Regular Carbonated Soft Drinks	37.3	299[4]
Energy Drinks	101.6	300
Flavored Water Drinks	172.2	205
Fruit Juice-Based Drinks, including concentrates	89.3	247
Ready-to-Drink Teas	73.5	197
Sports Drinks	0	0
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa[2]	0	0

GSFA = General Standard for Food Additives; na = not available; ppm = parts per million.

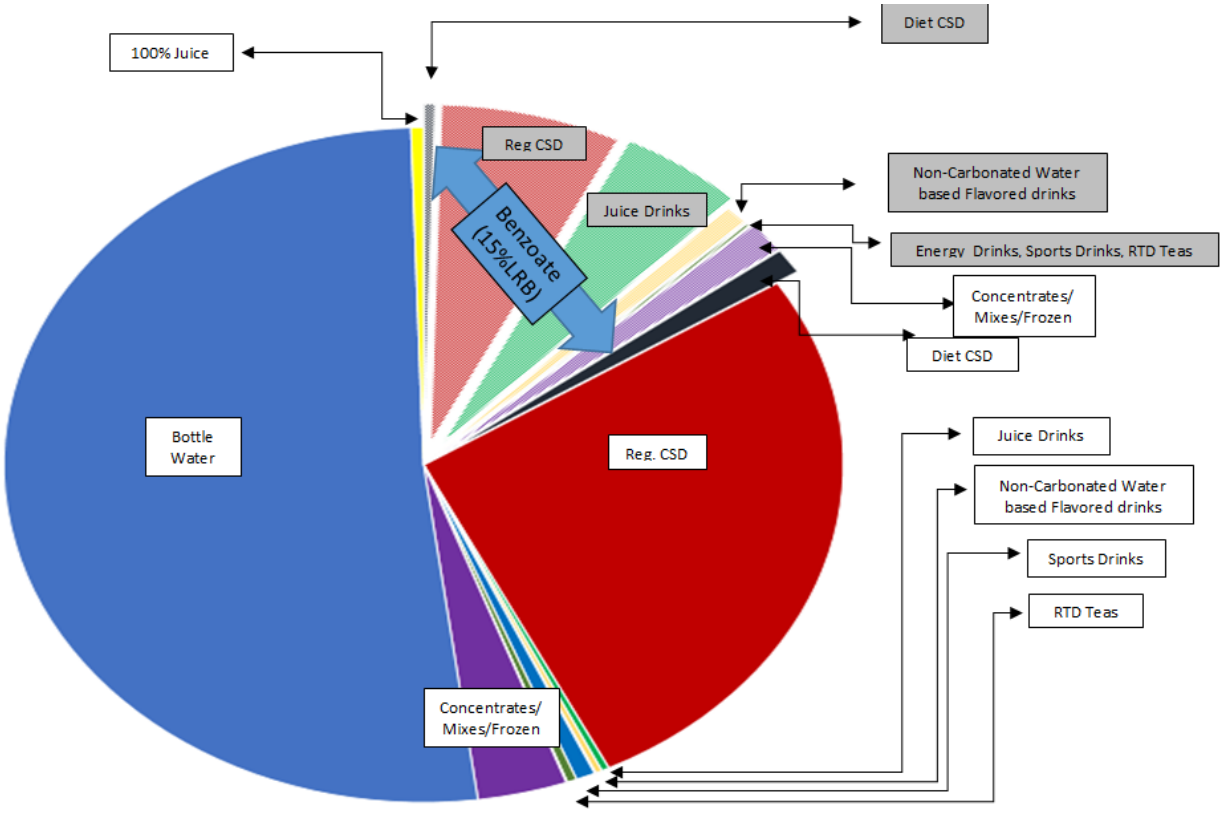
[1] No values were collated for the fruit juice concentrate category in 2016, therefore values obtained for '14.1.2.1 Fruit juice' *via* ICBA members were applied to the fruit juice concentrate category.

[2] Concentration data collected in 2014 for the fruit and vegetable nectar categories were applied here.

[3] As no data were reported for the fruit nectar concentrates category in 2014, the 2014 data on fruit nectars were applied here.

[4] Values were restricted to 250 ppm for beverages of pH ≤3.5 based on the Codex adopted interim level, in the 'brand-loyal model' only for the main contributing category (no use levels exceeding 250 ppm were reported for regular carbonated soft drinks of pH >3.5 in this jurisdiction). In contrast, **all** available use levels were used in the calculation of the market-weighted average use levels in this mode, and in the probabilistic model.

Figure 5.2-1 Distribution of Benzoate Use Among the Liquid Refreshment Beverage Sector in Mexico



5.3 Food Survey Results

Estimates based on the summary statistics rendered from the 24-hour food consumption data are presented in Section 5.3.1 (Deterministic Model 1). Estimates for the total daily intakes of benzoates based on the FFQ data are provided in Sections 5.3.2 (Probabilistic Model 2) and 5.3.3 (Brand-Loyal Distributional Model 3). All results are presented on a *per kilogram body weight* basis (mg/kg body weight/day). Detailed results regarding the estimated intake of benzoates from each food category in each age bracket for the latter two models are included as supplementary data in Appendix D.

5.3.1 Model 1 - Deterministic Assessment (24-Hour Recall)

Tables 5.3.1-1 and 5.3.1-2 below summarize the consumption estimates of individual beverage categories as reported by Stern *et al.* (2014), categorized according to GSFA beverage groups. The percent consumers, along with the *per capita* (general population) and consumer only consumption figures for each beverage type are available for children (aged 1 to 19 years) and adults (aged 20 years and over). The general population intakes from each individual beverage

category were summed in order to generate an estimate of the cumulative intake of benzoates from non-alcoholic beverages in children and adults.

For the consumer-only consumption figures from ENSANUT, there are no summary statistics available for 'total beverage' consumption by consumers, only the individual figures presented below. When the individual beverage consumption figures (mL/day) were summed, the resulting consumers-only total beverage consumption estimates were determined to be equivalent to 4.36 L/day for children and 5.09 L/day for adults. These figures, which relate only to non-water beverages, were considering to be unrealistic, particularly considering the Budget Method assumption regarding the theoretical maximum level of total non-milk beverages beverage consumption of 0.1 L per kg body weight (equivalent to 4.4 L of non-milk beverages for a 44.2 kg child; or 8.0 L on non-milk beverages) (WHO, 2009). Further, the percent consumers of the individual beverage categories ranged between 0.5 to 37.7% for children (Table 5.3.1-1) and 1.9 to 42.0% for adults (Table 5.3.1-2). As such, the possibility that an individual would consume at least one beverage from each category is highly unlikely. On this basis, the principles of the methodology employed in exposure assessments based on summary statistics - including the European Food Safety Authority (EFSA) Comprehensive Food Consumption Database (EFSA, 2011a) - were incorporated to obtain an estimate of 'high level' benzoate exposure. This approach assumes that a person may be reasonably assumed to be a heavy consumer of one food/beverage category and an average consumer of the remaining food/beverage categories. It is noted that the approach established by the EFSA Comprehensive Food Consumption Database utilizes the highest 95th percentile consumer only estimate for the 'heavy consuming' category, combined with the total population (*i.e.*, considering non-consumers) mean intakes for the remaining categories; however 95th percentile estimates were not available in the Stern *et al*., (2014) publication, as such, the highest 'consumer' intake (identified as "caloric soda") was summed with the general population intake for the remaining categories. Thus, the exposure results described in this section may be considered an upper estimate for consumer-only intake as part of the preliminary tier (deterministic) assessments for Mexico. Further details on the intakes by high consumers calculated using individual consumption data from the ENSANUT FFQ survey are described in Sections 5.3.2 and 5.3.3.

In order to generate estimates of intake on a body weight basis, anthropometric data from the ENSANUT database were employed to generate mean body weights for children aged 1 to 19 years and adults aged 20 years and older. Based on the available data, the mean body weight of children was calculated at 44.2 kg and the mean body weight of adults was calculated at 80.8 kg. These body weights were utilized to assess the daily intakes on a mg/kg body weight exposure levels for benzoates.

The interim ML of 250 ppm was applied to the consumption values for the largest contributing category in which benzoates was reportedly used ("Caloric soda"), and the market-weighted

average concentration was applied to all other categories. An individual is assumed to be brand-loyal to caloric soda beverages whilst consuming 'average' or typical levels all other beverage types (Model 1).

Amongst the general population, the total intake of benzoates from all beverage categories was estimated to be 1.2 mg/kg body weight/day; 24.1% ADI) in children aged 1 to 19 years (Table 5.3.1-1). When summating the consumer-only intake of the highest available contributing category (*i.e.*, caloric soda) with the mean intakes from the remaining beverage categories for the general population, the estimated consumer-only intake of benzoates among children aged 1 to 19 years was 2.4 mg/kg body weight/day (or 48% ADI). As previously noted, the total benzoate intake estimate among the consumer-only population was calculated by presuming that a person is a high consumer of one non-water beverage category and an average consumer of the remaining beverages since total beverage consumption figures are not available from the 24-hour recall phase of the 2012 ENSANUT study.

Table 5.3.1-1 Summary of the Estimated Exposure to Benzoates in Mexico by Children Aged 1 to 19 Years (2012 ENSANUT 24-Hour Recall Data)

GSFA Food Category	Beverage Category	General Population Exposure			Consumers Only Exposure			
		Beverage Category Intake (mL/day)	Estimated Benzoate Exposure Level		% Consumers	Beverage Category Intake (mL/day)	Estimated Benzoate Exposure Level	
			mg/day	mg/kg bw/day * (% ADI)			mg/day	mg/kg bw/day* (% ADI)
14.1.2 Fruit Juice	100% natural fruit and vegetable juice	10.6	0	0	3.0	347	0	0
	Fruit and Vegetable Drinks	54.9	0	0	18.9	290	0	0
14.1.4 Flavored Drinks	Flavored/Caloric Water	19.2	3.3	0.1	4.5	430	74.0	1.7
	Fruit Water	131	11.7	0.3	23.8	551	49.2	1.1
	Caloric Soda[1]	131	32.8	0.7	37.7	348	87.0	2.0
	Low Calorie Soda	28.5	4.8	0.1	8.3	342	57.9	1.3
	Sports and Energy Drinks	3.1	0.3	<0.1	0.5	586	59.5	1.3
	Other Beverages	5.0	0.4	<0.1	3.3	150	11.0	0.2

Table 5.3.1-1 Summary of the Estimated Exposure to Benzoates in Mexico by Children Aged 1 to 19 Years (2012 ENSANUT 24-Hour Recall Data)

GSFA Food Category	Beverage Category	General Population Exposure			Consumers Only Exposure			
		Beverage Category Intake (mL/day)	Estimated Benzoate Exposure Level		% Consumers	Beverage Category Intake (mL/day)	Estimated Benzoate Exposure Level	
			mg/day	mg/kg bw/day * (% ADI)			mg/day	mg/kg bw/day* (% ADI)
14.1.5 Coffee	Caloric Coffee and Tea	62.4	0	0	21.7	287	0	0
	Plain Coffee and Tea	41.4	0	0	11.6	358	0	0
	Milk-Based Atole	13.7	0	0	4.3	317	0	0
	Water-Based Atole	12.3	0	0	3.5	355	0	0
Totals			**53.3**	**1.2 (24.1%)**			**107.5[2]**	**2.4[2] (48%)**

Source: Stern *et al.* (2014).
bw = body weight; cons = consumers; ENSANUT = Encuesta Nacional de Salud y Nutrición.
* A mean body weight of 44.2 kg was utilized to estimate benzoate intake on a *per kilogram body weight* basis.
[1] Identified as the highest contributing beverage category to benzoate intakes.
[2] Value calculated by summing the intakes from the highest contributing food category and the mean general population exposure values for the remaining categories.

When considering adults aged 20 years and older, the total general population intake of benzoates from all beverage categories was estimated to be 0.9 mg/kg body weight/day (17.9% ADI) (Table 5.3.1-2). Among adults, the estimated consumer-only intake of benzoates was calculated to be 1.7 mg/kg body weight/day (34% ADI or 141.4 mg/day on an absolute basis).

Table 5.3.1-2 Summary of the Estimated Exposure to Benzoates in Mexico by Adults Aged 20 Years and Older (2012 ENSANUT 24-Hour Recall Data)

GSFA Food Category	Beverage Category	General Population Exposure			Consumers Only Exposure			
		Beverage Category Intake (mL/day)	Estimated Benzoate Exposure Level		% Cons	Beverage Category Intake (mL/day)	Estimated Benzoate Exposure Level	
			mg/day	mg/kg bw/day*			mg/day	mg/kg bw/day*
14.1.2 Fruit Juice	100% natural fruit and vegetable juice	19.8	0	0	4.1	482	0	0
	Fruit and Vegetable Drinks	23.3	0	0	6.9	337	0	0

Table 5.3.1-2 Summary of the Estimated Exposure to Benzoates in Mexico by Adults Aged 20 Years and Older (2012 ENSANUT 24-Hour Recall Data)

GSFA Food Category	Beverage Category	General Population Exposure			Consumers Only Exposure			
		Beverage Category Intake (mL/day)	Estimated Benzoate Exposure Level		% Cons	Beverage Category Intake (mL/day)	Estimated Benzoate Exposure Level	
			mg/day	mg/kg bw/day*			mg/day	mg/kg bw/day*
14.1.4 Flavored Drinks	Flavored/Caloric Water	16.9	2.9	0.0	3.6	470	80.9	1.0
	Fruit Water	138	12.3	0.2	21.9	630	56.3	0.7
	Caloric Soda[1]	201	50.3	0.6	42.0	478	119.5	1.5
	Low Calorie Soda	34.4	5.8	0.1	8.3	415	70.3	0.9
	Sports and Energy Drinks	5.7	0.6	<0.1	1.0	555	56.4	0.7
	Other Beverages	3.4	0.2	<0.1	2.0	174	12.8	0.2
14.1.5 Coffee	Caloric Coffee and Tea	129	0	0	37.6	342	0	0
	Plain Coffee and Tea	93.9	0	0	22.9	410	0	0
	Milk-Based Atole	15.6	0	0	4.5	324	0	0
	Water-Based Atole	21.4	0	0	4.5	474	0	0
Total			**72.1**	**0.9 (17.9%)**			**141.4[2]**	**1.7[2] (34%)**

Source: Stern *et al.* (2014).
bw = body weight; cons = consumers; ENSANUT = Encuesta Nacional de Salud y Nutrición.
* A mean body weight of 80.8 kg was utilized to estimate benzoate intake on a *per kilogram body weight* basis.
[1] Identified as the highest contributing beverage category to benzoate intakes.
[2] Value calculated by summing the intakes from the highest contributing food category and the mean general population exposure values for the remaining categories.

5.3.2 Model 2 - Probabilistic Assessment (FFQ)

Table 5.3.2-1 summarizes the estimated total intake of benzoates (mg/kg body weight/day; % ADI) from the full range of reported benzoate use levels from non-alcoholic beverages in Mexico when calculated using individual-based data from the FFQ.

The total mean and 95th percentile intakes were estimated to be 0.5 and 2.5 mg/kg body weight/day, respectively (9.8 to 10.5% and 49.1 to 51.0% of the ADI, respectively), irrespective of whether the general population or consumers only were examined. The general population and consumer only intakes were similar among all age groups, ranging between 0.4 to 0.9 mg/kg body weight/day (7.7 to 17.0% ADI) at the mean and 2.0 to 3.7 mg/kg body weight/day (39.7 to 74.2% ADI) at the 95th percentile.

The results presented in Appendix D.1 demonstrate that even when exposure levels are examined by individual age groups and for specific beverage types, the ADI was not exceeded by any population group.

Table 5.3.2-1 Summary of the Estimated Exposure to Benzoates from Reported Use Levels in Beverages in Mexico by Population Group (2012 ENSANUT FFQ Data) - Probabilistic Model

Population Group	Age Group (Years)	Number of Individuals Surveyed[1]	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
			Mean (% ADI)	95th Percentile (% ADI)	Mean (% ADI)	95th Percentile (% ADI)
Toddlers and Young Children	1 to 7	1,678	0.8 (16.0)	3.7 (74.0)	0.9 (17.0)	3.7 (74.2)
Other Children, Including Adolescents	8 to 17	2,525	0.6 (12.2)	2.9 (57.4)	0.6 (12.9)	3.0 (59.0)
Adults	18 and Older	3,194	0.4 (7.7)	2.0 (39.7)	0.4 (8.3)	2.1 (41.4)
Total Population	All Ages	7,397	0.5 (9.8)	2.5 (49.1)	0.5 (10.5)	2.5 (51.0)

bw = body weight; ENSANUT = Encuesta Nacional de Salud y Nutrición; FFQ = food frequency questionnaire.
[1] The probabilistic assessment was conducted using a target of 100,000 person-days; equivalent to approximately 13 iterations of the ENSANUT FFQ.

5.3.3 Model 3 - Brand-Loyal Distributional Assessment (FFQ)

Table 5.3.3-1 summarizes the estimated total intake of benzoates (mg/kg body weight/day; % ADI) from non-alcoholic beverages in Mexico, considering the interim ML of 250 ppm adopted by Codex within regular carbonated soft drinks[13] and the market-weighted average use levels among the remaining categories.

In the general population, estimates of the mean and 95th percentile benzoate intakes were 1.2 and 4.3 mg/kg body weight/day among all ages (representing 24.8 and 86.2% of ADI), respectively. The mean and 95th percentile intakes of benzoates were 1.3 and 4.4 mg/kg body weight/day (26.4 and 88.6% ADI), respectively, among consumers-only. As with Model 2, toddlers and young children were identified as having the highest mean and 95th percentile all-user intakes of any age group, at 1.7 and 5.3 mg/kg body weight/day (33.4 and 105.4% ADI), respectively. Those brand-loyal toddlers and young children slightly exceeding the ADI who are assumed to be habitual consumers of regular carbonated soft drinks containing the maximum amount of benzoates at 250 ppm correspond to 75 toddlers/children out of 1,678 toddlers/children surveyed (*i.e.*, 4.5%) and out of all 7,397 respondents surveyed (*i.e.*, 1%) in

[13] No regular carbonated soft drinks of pH >3.5 had a reported use level exceeding 250 ppm in this jurisdiction, further, no food codes were available which represented these beverage types.

ENSANUT and represent a conservative scenario. Estimated intakes among consumers in the other age groups ranged between 1.2 and 1.6 mg/kg body weight/day (23.2 and 31.0% ADI) at the mean, and 4.0 and 4.8 mg/kg body weight/day (79.4 and 96.2% ADI) at the 95th percentile.

The results presented in Appendix D.2 demonstrate that even when exposure levels are examined by individual age groups and for specific beverage types, the ADI was not exceeded by any population group.

Table 5.3.3-1 Summary of the Estimated Exposure to Benzoates from Reported Use Levels in Beverages in Mexico by Population Group (2012 ENSANUT FFQ Data) - Brand-Loyal Distributional Model

Population Group	Age Group (Years)	Number of individuals surveyed	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
			Mean (% ADI)	95th Percentile (% ADI)	Mean (% ADI)	95th Percentile (% ADI)
Toddlers and Young Children	1 to 7	1,678	1.6 (31.4)	5.1 (101.6)	1.7 (33.4)	5.3 (105.4)
Other Children, Including Adolescents	8 to 17	2,525	1.5 (29.4)	4.8 (96.0)	1.6 (31.0)	4.8 (96.2)
Adults	18 and Older	3,194	1.1 (21.6)	3.8 (76.0)	1.2 (23.2)	4.0 (79.4)
Total Population	All Ages	7,397	1.2 (24.8)	4.3 (86.2)	1.3 (26.4)	4.4 (88.6)

ADI = acceptable daily intake; bw = body weight; ENSANUT = Encuesta Nacional de Salud y Nutrición; FFQ = food frequency questionnaire

5.3.3 Proportion of Consumers of Individual Beverage Categories (FFQ Assessments)

Estimates for the mean and 95th percentile daily intakes of benzoates from each individual non-alcoholic beverage category are summarized in the tables included in Appendix D, for both the probabilistic and the brand-loyal distributional models. The total Mexican population (all ages) was identified as being significant consumers of regular carbonated soft drinks (73.7%)[14], fruit juice-based drinks (38.3%) and flavoured water drinks (17.3%). It is noted that in the brand loyal model, the 73.7% consumers of regular carbonated soft drinks were selected to be brand-loyal to regular carbonated soft drinks containing the maximum benzoate levels of 250 ppm per the Codex adopted interim level.

[14] The proportion of consumers among toddlers and children, other children and adolescents, and adults were 72.6%, 76.8%, and 72.8%, respectively. Due to the limited food codes available in the ENSANUT survey, it is noted that only one food code was available to represent all “regular sodas”.

5.3.4 Contribution of Each Beverage Category to Total Intakes (FFQ Assessments)

As benzoate use was reported to be "0" in GSFA categories 14.1.2, 14.1.3, and 14.1.5 - *i.e.*, juices, nectars, coffee/tea, respectively - these particular beverages did not contribute benzoate intakes in the various models created (*i.e.* all intakes originated from the consumption of products classified under GSFA category 14.1.4). Within the arbitrary subcategories of 14.1.4, regular soft drinks contributed 43.7% to overall total intakes in the probabilistic intake model (Model 2) and to 72.5% of total intakes in the brand loyal distributional model (Model 3) among all ages. Within toddlers and young children, specifically being identified as potentially having higher intakes than the rest of the population groups examined, regular carbonated soft drinks accounted for 19.6% of total mean benzoate intakes in the probabilistic intake model (which includes the full spectrum of reported benzoate use levels in the model) and to 62.8% of total intakes in the brand loyal distributional model (having only the interim ML of 250 ppm represented in the model for regular CSDs, with a market-weighted average for all other categories).

5.4 Conclusions for the Intakes of Benzoates in Mexico

The current exposure assessment has assessed intakes among the Mexican population using actual use level data reported by members of the ICBA for beverages combined with summary statistics for the 24-hour diet recall (Model 1) and individual food consumption data from the ENSANUT 2012 FFQ (Models 2 and 3).

Utilizing the 24-hour recall data (Model 1), the mean general population estimate of benzoate intakes was 1.2 (24.1% ADI) among children (1 to 19 years) and 0.9 mg/kg body weight/day (17.9% ADI), among adults (20+ years). These general population estimates are based on a model in which the interim Codex ML of 250 ppm was applied to the consumption value for the largest contributing category ("Caloric soda"), and the market-weighted mean benzoate use level was applied to all other categories, thereby assuming an individual may be brand-loyal to caloric soda beverages, whilst still consuming all other beverage types. Due to the absence of total non-alcoholic beverage consumption estimates among consumers only, the consumer-only total mean was derived by summating the intakes from the highest contributing beverage category, caloric soda, with the mean consumption of the remaining beverage categories among the general population. The estimates of consumer only exposure among children aged 1 to 19 years and among adults aged 20 years and older employing this method were 2.4 mg/kg body weight/day (48% ADI) and 1.7 mg/kg body weight/day (34% ADI), respectively.

Every brand-specific benzoate use level and branded beverage market share was incorporated in the probabilistic assessment utilizing consumption data derived from the FFQ phase of the ENSANUT study (Model 2). The assessment rendered mean and 95th percentile consumer-only estimates of 0.5 and 2.5 mg/kg body weight/day among all ages (10.5 and 51.0% ADI),

respectively. A third model was conducted, which mirrored Model 1 above, in that individuals were assumed to be brand-loyal to the highest contributing beverage category of regular carbonated soft drinks; however, individual food consumption data from the FFQ was leveraged to produce estimates of intake, as opposed to 24-hour recall summary statistics in the case of Model 1 (providing a more realistic estimate of exposure on an individual level). The mean and 95th percentile consumer-only estimates were calculated as 1.3 and 4.4 mg/kg body weight/day among all ages (26.4 and 88.6% ADI), respectively. The ADI was marginally exceeded at the 95th percentile of consumption among toddlers and young children, with intakes reaching 5.3 mg/kg body weight/day (105.4% ADI) in this age group, assuming individuals in this age group were heavy consumers of regular carbonated soft drinks containing benzoates at the interim ML of 250 ppm with a 100% presence probability.

6.0 BRAZIL

6.1 Food Consumption Survey Data

6.1.1 Survey Description

Food consumption data in Brazil was based on summary statistics reports generated from the Pesquisa de Orçamentos Familiares (POF; Household Budget Survey; 2008-2009), a household income and expenditure survey designed to be conducted every 5 years by the Instituto Brasileiro de Geografia e Estatistica (IBGE). Within the 2008-2009 Household Budget Survey, a National Dietary Survey (Inquérito Nacional de Alimentação) was intended to collect data on individual dietary intake. The IBGE presented an analysis of the food consumption among individuals aged 10 years or over in Brazil on a *per capita* basis (IBGE, 2014). Each respondent surveyed was instructed to complete records of all food and beverages consumed (except water) inside and outside of the house for 2 non-consecutive days in both urban and rural areas for 24 hours. The methodology was based on additional sources, which included the *Table of Reference Measures for Food Consumed in Brazil*, *Tables of the Nutritional Composition of food Consumed in Brazil*, both resulting from the 2008-2009 POF, as well as technical and scientific publications (IBGE, 2014). It should be noted that most of the data were transcribed from documents originally provided in Portuguese (POF, 2011).

The POF consisted of 2 stages following geographical and statistical stratification of the primary sample units (PSU) using the 2000 Brazilian Demographic Census (Souza *et al*., 2013). The PSUs were selected in the first stage with probability proportional to the number of residences in each sector. Based on simple random sampling in each stratum, a subsample of sectors was selected (Souza *et al*., 2013). In the second stage, households were selected based on simple random sampling and without replacement in each of the PSUs. To ensure that all of the geographic and socio-economic strata were represented, the primary sample units were assessed throughout the 12 months of the survey (four 3-month periods) (Souza *et al*., 2013).

The response rate of the POF was 60.7%, equivalent to 55,970 households. A subsample of the households (25%; n=13,569) was randomly selected to provide food consumption data, which was equivalent to approximately 34,003 individuals (Souza *et al*., 2013; IBGE, 2014).

Individuals reported all foods and beverages consumed, including portion sizes, over 2 non-consecutive days using food records (Souza *et al*., 2013). If the survey respondent was unable to complete the food record, another resident in the household or someone indicated by the survey respondent completed the food record on their behalf. Data were stored in a specifically designed program which comprised of approximately 1,500 food and drink items from the 2002-2003 POF database, the program also contained methods of preparation and pre-defined portion sizes. Summary statistics were published for these pre-determined food and beverage items, and estimates pertaining to the intake of any beverage types which were deemed relevant were extracted for the current analysis. The following beverage items were selected:

- Juices, refreshments, juice powder reconstituted
- Soft drinks
- Soft drinks (diet/light)
- Other nonalcoholic beverages
- Coffee
- Tea

The data presented in this section is based on reported values for percent consumption and average *per capita* (general population) intakes of the above-listed beverage categories by participants of the POF survey.

6.1.2 Statistical Methods

Two exposure assessment models were employed for the evaluation of intakes of benzoates in Brazil.

1. Deterministic exposure assessment using a maximum benzoate use level of 250 ppm (the interim ML adopted by Codex). It is noted that the nature of the beverage consumption data available is not amenable to building in considerations to account for market share, nor beverage categories in which only a subsector had reported benzoate use. Thus, the calculated benzoate intakes are considered an overestimate of actual exposure by this population group.

2. Deterministic brand loyal assessment: Beverage categories were assumed to contain benzoates at a market-weighted average, with the exception of the highest consumed beverage category, “juices/refreshments/juice powder reconstituted”, to which a

benzoate concentration level of 250 ppm was applied across the entire category in spite of the fact that only “refreshments” (and not juices or juice powder) were reported to contain benzoates.

In both models, the total cumulative exposure level for benzoates has been determined by summing the exposure value for each individual beverage category.

6.1.3 Food Consumption Data

As mentioned above, data were only available for aggregated, pre-determined beverage categories for Brazil from the POF. For the largest contributing category, “juices/refreshments/juice powder reconstituted”, it is noted that the concentration data submitted for GSFA categories 14.1.2.1, 14.1.2.3, 14.1.3.1, and 14.1.3.3 (*i.e.*, juices and nectars) indicate that no benzoates are used in these product types (see Section 6.2). However, benzoate use *was* reported for fruit-flavored drinks and juice drinks (falling under GSFA category 14.1.4). Due to the nature of the POF categorizations, it was considered appropriate to apply the worst-case presence of 250 ppm benzoate use to the “juices/refreshments/juice powder reconstituted” category in order to capture potential exposure from these beverage products. This is a conservative assumption. Fruit-flavoured drinks would account for only a proportion of the reported consumption for this broader beverage category (see Appendix G for the full food code list that was included in the POF evaluation).

6.2 Concentration Data

Concentration data on benzoate use levels in non-alcoholic beverages (on a benzoic acid basis) were collated by the ICBA with the aid of the Brazilian Association of Soft Drink and Non-Alcoholic Beverages (ABIR). A market-weighted average benzoate use level was determined based on country-specific and brand-specific use levels and brand market share in Brazil. The highest reported concentration of benzoate use in Brazil was identified for each beverage category, and in instances where the industry-reported maximum exceeded 250 ppm[15], the value was lowered so as to not exceed these levels based on the interim ML established by Codex. Due to the inherit limitations of a deterministic exposure assessment (*i.e.*, application of one fixed concentration to a fixed consumption value) and the large assortment of beverage types encompassed in the summary consumption statistics available for Brazil (see ‘POF food category’ types listed in Table 6.3.1.1-1 and 6.3.1.1-2) , as noted above, it was determined to be most appropriate to apply the interim ML of 250 ppm to the large aggregate beverage categories representative of category 14.1.4 in Model 1; or to “Refreshments, Juices powder reconstituted” in Model 2. Further, the models presented herein

[15] Beverages with a pH >3.5 represented less than 1% of the market share; thus, a limit of 250 ppm was considered most appropriate for this model.. Further, no consumption data was available for beverages which may have a pH greater than 3.5 in the POF.

assumed 100% presence probability, whereas, it is noted that the majority of products are reported to *not* contain benzoates (see Figure 6.2-1).

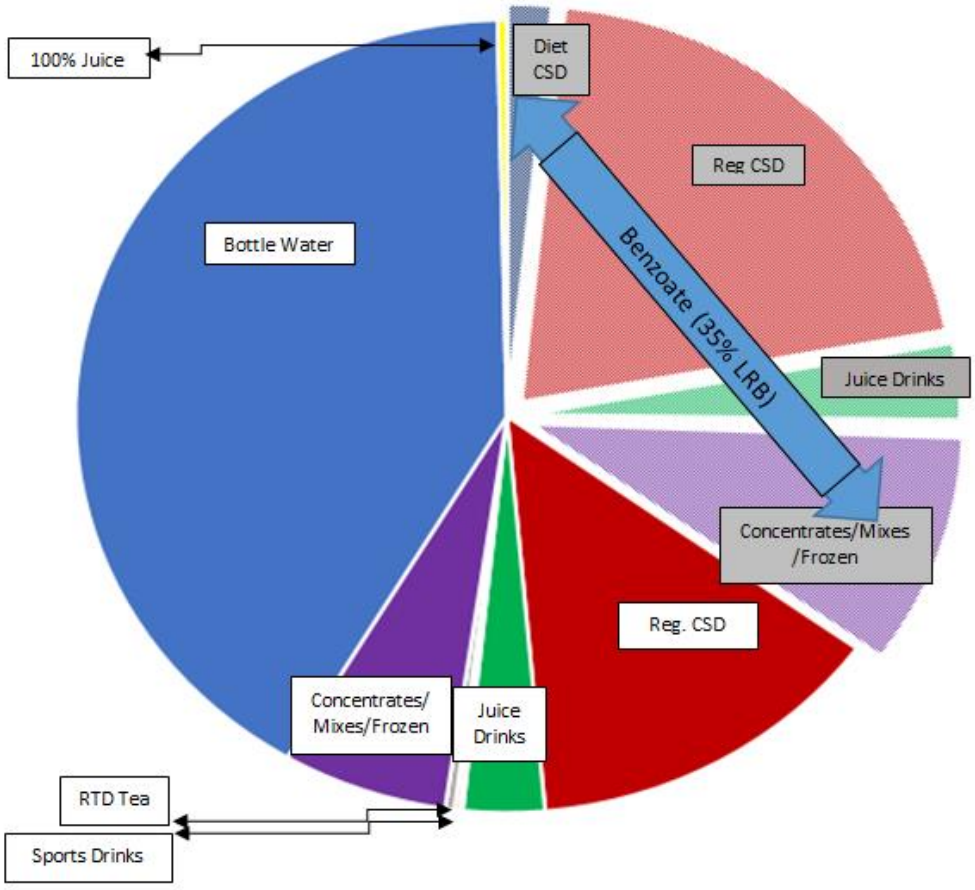
No market-weighted mean concentrations of benzoate use levels exceeded 250 ppm and therefore, individual concentrations submitted to the ICBA were not altered when calculating the market-weighted mean values (see Table 6.2-1).

Table 6.2-1 Weighted Average and Maximum Reported Use Levels of Benzoate in Brazil, by Codex GSFA Food Category

GSFA Food Category	Benzoates Use Level (ppm)	
	Market-Weighted Average Use Level	Highest Reported Typical Level
14.1.2.1 Fruit Juice	0	0
14.1.2.3 Concentrates for Fruit Juice[1]	0	0
14.1.3.1 Fruit Nectar[2]	0	0
14.1.3.3 Concentrates for Fruit Nectar[3]	0	0
14.1.3.4 Concentrates for Vegetable Nectars[4]	na	na
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks		
Diet Carbonated Soft Drinks	185.6	297[5]
Regular Carbonated Soft Drinks	82.7	297[5]
Energy Drinks	144.0	366[5]
Flavoured Water Drinks	0	0
Fruit Juice-Based Drinks, including concentrates	75.6	339[5]
Ready-to-Drink Teas	66.0	271[5]
Sports Drinks	38.5	263[5]
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa[6]	0	0

GSFA = General Standard for Food Additives; na = not available; ppm = parts per million.
[1] No values were collated for the fruit juice concentrate category in 2016, therefore values from '14.1.2.1 Fruit juice' *via* ICBA members were applied here.
[2] Value was based on feedback from ICBA members.
[3] No values were collated for fruit nectar concentrate category; therefore, values from '14.1.3.1 Fruit nectar' were applied here.
[4] No data were reported for the vegetable nectar concentrate category in 2014, thus data for other nectars were applied here.
[5] Values were restricted to 250 ppm for all beverage types due to the nature of the aggregated beverage consumption statistics available for Brazil; No use levels exceeding 250 ppm were reported for beverages of pH >3.5 in this jurisdiction.
[6] Levels reflected here correspond to data collected in 2014.

Figure 6.2-1 Distribution of Benzoate Use Among the Liquid Refreshment Beverage Sector in Brazil



6.3 Food Survey Results

Estimates for the daily intakes of benzoates from the two deterministic models employed are presented in Sections 6.3.1 (maximum benzoate use levels of 250 ppm) and 6.3.2 (brand-loyal assessment). Results are expressed in terms of *per capita* (general population) mean and heavy level (90th percentile, not 95th percentile as the latter was not available) intakes, stratified across the total population, gender (males/females), and age brackets (teenagers, adults and elderly adults). Since Brazil collected consumption data for individuals 10 years and older, an evaluation for toddler/children as defined by JECFA (*i.e.*, 1 to 7 years) was not possible. Weighted mean body weight estimates were derived from the median body weights reported by the POF, and the population statistics of the study, in order to calculate a weighted average body weight. The full calculation is provided in Appendix F. These values were used to calculate the average *per capita* intake figures on a *per kilogram body weight* basis, and expressed as a proportion of the ADI.

6.3.1 Model 1 - Deterministic Assessment at 250 ppm Benzoate Use

Because POF summary data are arranged according to mean and 90th percentiles of intake (as explained above), and stratified among population groups therein, estimates of mean and 90th percentile intake of benzoates are presented separately in Sections 6.3.1.1 and 6.3.1.2, respectively.

6.3.1.1 Mean Intake

Tables 6.3.1.1-1 and 6.3.1.1-2 summarize the estimated total general population mean intake of benzoates, stratified by gender and age groups, respectively, calculated using the deterministic maximum model.

The total mean general population intakes of benzoates within the total population (all ages and genders) were calculated to be 0.97 mg/kg body weight/day (19.5% ADI). The calculated intakes for the two gender groups were nearly identical on a body weight basis at 1.0 mg/kg body weight/day (20.1% ADI) for males and 0.95 mg/kg body weight/day (18.9% ADI) for females (Table 6.3.1.1-1).

Table 6.3.1.1-1 Reported Percent Consumption and Average *Per capita* Consumption of Beverage Categories and Calculated Exposure to Benzoates by the Total Population and Split by Gender (POF 2008-2009) – Deterministic Maximum Model

GSFA Food Category	POF Food Category	Reported Food Category Intakes		Calculated Exposure to Benzoates	
		% cons	g/day	(mg/day)[1]	mg/kg bw/day (% ADI)[2]
Total Population					
14.1.2.1 Fruit Juice	Juices	39.8	145.0	36.3	0.57
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks	Refreshments, juice powder reconstituted				
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks	Soft drinks	23.0	94.7	23.7	0.37
	Soft drinks (diet/light)	1.6	5.5	1.4	0.02
	Other nonalcoholic beverages	0.8	2.7	0.7	0.01
	Coffee	79.0	215.1	0	0

Table 6.3.1.1-1 Reported Percent Consumption and Average *Per capita* Consumption of Beverage Categories and Calculated Exposure to Benzoates by the Total Population and Split by Gender (POF 2008-2009) – Deterministic Maximum Model

GSFA Food Category	POF Food Category	Reported Food Category Intakes		Calculated Exposure to Benzoates	
		% cons	g/day	(mg/day)[1]	mg/kg bw/day (% ADI)[2]
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Tea	6.0	31.3	0	0
Total mean general population intakes[3]				**62.0**	**0.97 (19.5%)**
Males					
14.1.2.1 Fruit Juice	Juices	38.8	151.8	38.0	0.56
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks	Refreshments, juice powder reconstituted				
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks	Soft drinks	24.8	112.2	28.1	0.41
	Soft drinks (diet/light)	1.3	5.2	1.3	0.02
	Other nonalcoholic beverages	1.0	3.2	0.8	0.01
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Coffee	78.7	222.3	0	0
	Tea	4.3	26.8	0	0
Total mean general population intakes (male)[3]				**68.1**	**1.00 (20.1%)**
Females					
14.1.2.1 Fruit Juice	Juices	40.7	138.7	34.7	0.58
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks	Refreshments, juice powder reconstituted				

Table 6.3.1.1-1 Reported Percent Consumption and Average *Per capita* Consumption of Beverage Categories and Calculated Exposure to Benzoates by the Total Population and Split by Gender (POF 2008-2009) – Deterministic Maximum Model

GSFA Food Category	POF Food Category	Reported Food Category Intakes		Calculated Exposure to Benzoates	
		% cons	g/day	(mg/day)[1]	mg/kg bw/day (% ADI)[2]
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Soft drinks	21.2	78.4	19.6	0.33
	Soft drinks (diet/light)	1.8	5.8	1.5	0.02
	Other nonalcoholic beverages	0.7	2.2	0.6	0.01
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Coffee	79.3	208.4	0	0
	Tea	7.6	35.5	0	0
Total mean general population intakes (female)[3]				**56.3**	**0.95 (18.9%)**

% cons = percent consumption of food category; ADI = acceptable daily intake; GSFA = Codex General Standard for Food Additives; POF = Pesquisa de Orçamentos Familiares (Household Budget Survey).
[1] Calculated as: [reported consumption] x [benzoate use level]. See Table 6.2-1 for concentrations utilized.
[2] See Appendix F for calculation of weighted mean body weight per age group (63.6 kg for total population; 67.9 kg for males and 59.5 kg for females).
[3] Calculated as: the sum of individual intakes calculated for each POF food category.

Estimates for mean general population intakes also were presented with stratification for age category available from the POF, namely teenagers (ages 10 to 18 years), adults (ages 19 to 59 years), and elderly adults (ages 60 years and older). The POF did not have age stratification, or indeed consumption data, for brackets younger than 10 years of age. The highest estimated cumulative mean exposure to benzoates were identified in teenagers on a body weight basis, at 1.34 mg/kg body weight/day (26.7 % ADI), which remained a very small fraction of the ADI even when considering the maximum benzoate use level of 250 ppm in all beverage categories. The mean adults and elderly general population intake amounts were estimated to be 0.94 mg/kg body weight/day (18.8% ADI) and 0.55 mg/kg body weight/day (10.9% ADI), respectively (Table 6.3.1.1-2).

Table 6.3.1.1-2 Reported Percent Consumption and Average *Per capita* Consumption of Beverage Categories and Calculated Benzoate Intakes by Teenagers, Adults, and Elderly Adults (POF 2008-2009) - Deterministic Maximum Model

GSFA Food Category	POF Food Category	Reported Food Category Intakes		Calculated Benzoate Intakes	
		% cons	g/day	(mg/day)[1]	mg/kg bw/day (% ADI)[2]
Teenagers					
14.1.2.1 Fruit Juice	Juices	43.7	167.8	42.0	0.75
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Refreshments, juice powder reconstituted				
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Soft drinks	28.2	123.7	30.9	0.56
	Soft drinks (diet/light)	1.2	4.1	1.0	0.02
	Other nonalcoholic beverages	0.5	1.5	0.4	0.01
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Coffee	62.8	166.7	0	0
	Tea	3.4	10.4	0	0
Total mean general population intakes (teenagers)				**74.3**	**1.34 (26.7%)**
Adults					
14.1.2.1 Fruit Juice	Juices	40.3	147.4	36.9	0.54
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Refreshments, juice powder reconstituted				
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Soft drinks	23.7	98.2	24.6	0.36
	Soft drinks (diet/light)	1.7	6.3	1.6	0.02
	Other nonalcoholic beverages	1.2	3.0	0.8	0.01
	Coffee	82.2	222.8	0	0

Table 6.3.1.1-2 Reported Percent Consumption and Average *Per capita* Consumption of Beverage Categories and Calculated Benzoate Intakes by Teenagers, Adults, and Elderly Adults (POF 2008-2009) - Deterministic Maximum Model

GSFA Food Category	POF Food Category	Reported Food Category Intakes		Calculated Benzoate Intakes	
		% cons	g/day	(mg/day)[1]	mg/kg bw/day (% ADI)[2]
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Tea	5.9	34.4	0	0
Total mean general population intakes (adults)				**63.7**	**0.94 (18.8%)**
Elderly					
14.1.2.1 Fruit Juice	Juices	31.3	100.2	25.1	0.38
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks	Refreshments, juice powder reconstituted				
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks	Soft drinks	11.4	35.1	8.8	0.13
	Soft drinks (diet/light)	1.4	3.8	1.0	0.01
	Other nonalcoholic beverages	1.2	3.0	0.8	0.01
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Coffee	86.6	246.9	0	0
	Tea	10.0	46.0	0	0
Total mean general population intakes (elderly)				**35.5**	**0.55 (10.9%)**

% cons = percent consumption of food category; ADI = acceptable daily intake; GSFA = General Standard for Food Additives; POF = Pesquisa de Orçamentos Familiares (Household Budget Survey).
[1] Calculated as: [reported consumption] x [benzoate use level]. See Table 6.2-1 for concentrations utilized.
[2] See Appendix F for calculation of weighted mean body weight per age group (55.63 kg for teenagers; 67.83 kg for adults; and 65.11 kg for the elderly).
[3] Calculated as: the sum of individual intakes calculated for each POF food category.

6.3.1.2 90th Percentile Intake

Intakes at the 10th, 50th and 90th percentile were reported for a number of POF food categories for males and females separately (a 95th percentile figure was not available for use and no other

population sub-groups were analyzed[16]). The percentile distribution was calculated taking into account the intra-individual consumption variability using information from 2 days to selected food groups. The 90th percentile consumption is presented for the categories 'Juices' and 'Soft Drinks', as shown in Table 6.3.1.2-1. As mentioned in Section 6.2, benzoates are reported not to be used in fruit juices. As such, high level exposures to benzoate from soft drinks alone are considered herein. The 90th percentile exposure level for males and females from soft drinks is estimated at 1.07 and 0.93 mg/kg body weight/day, respectively, equivalent to 21.4 and 18.6% ADI.

Table 6.3.1.2-1 Reported 90th Percentile Consumption for Beverage Categories for Males and Females (POF 2008-2009) and Calculated Intakes of Benzoates - Maximum Use Levels

GSFA Food Category	POF Food Category	Reported 90th Percentile Food Category Intakes	Calculated 90th Percentile Benzoate Intakes	
		g/day	mg/day[1]	mg/kg bw/day (% ADI)[2]
Males				
14.1.2.1 Fruit Juice	Juices	293.3	0	0
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Soft Drinks	290.6	72.7	1.07
Total 90th percentile intakes (males)			**72.7**	**1.07 (21.4%)**
Females				
14.1.2.1 Fruit Juice	Juices	273.6	0	0
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Soft Drinks	222.1	55.5	0.93
Total 90th percentile intakes (females)			**55.5**	**0.93 (18.6%)**

ADI = acceptable daily intake; GSFA = Codex General Standard for Food Additives; POF = Pesquisa de Orçamentos Familiares (Household Budget Survey)
[1] Calculated as: [reported consumption] x [benzoate use level]. See Table 6.2-1 for concentrations utilized.
[2] See Appendix F for calculation of weighted mean body weight per age group (67.9 kg for males and 59.5 kg for females)

6.3.2 Model 2 - Deterministic Brand Loyal Assessment

A brand-loyal deterministic assessment was developed by first establishing the main contributing category, which for this particular jurisdiction was identified to be the beverage aggregate comprising of "Juice/refreshments/juice powder reconstituted". This differs from other jurisdictions, in which regular carbonated soft drinks were selected as the brand loyal

[16] Heavy-level consumption for age brackets were not reported in the POF publication and therefore no further estimates of heavy-level intakes in the Brazilian population based on POF statistics were feasible.

category. This difference is presumed to be due to the broad categorization system available for the POF summary statistics. The maximum benzoate use level of 250 ppm per the Codex adopted interim level for benzoates was assigned to this beverage category, whilst using the market-weighted mean benzoate concentrations among the other POF beverage categories.

The 90th percentile calculation for the deterministic (non-brand-loyal) assessment presented in Section 6.3.1.2 above was based on the application of the interim ML to the available consumption data for 'soft drinks' and assignment of 0 ppm to 'juices'. Based on the limited nature of the summary statistics for high level intakes (*i.e.*, only available for 'soft drinks' and 'juices'), the identical approach would be taken for a 'brand loyal' individual. As such 'high level' intakes are not duplicated in this section. Only the mean benzoates exposure level is presented for the brand-loyal model below.

6.3.2.1 Mean Intake

Tables 6.3.2.1-1 and 6.3.2.1-2 summarize the estimated total general population mean intakes of benzoates, stratified by gender and age groups, respectively.

When considering a market-weighted mean benzoate concentration and a maximum use level of 250 ppm among "Juice/refreshments/juice powder reconstituted", the total mean general population exposure for the entire population group (all ages and genders), and when split by gender, was 0.71 mg/kg body weight/day (14.3% ADI).

Table 6.3.2.1-1 Reported Percent Consumption and General Population Consumption of Beverage Categories and Calculated Exposure to Benzoates by the Total Population and Split by Gender (POF 2008-2009) - Brand-Loyal Assessment

GSFA Food Category	POF Food Category	Reported Food Category Intakes		Calculated Exposure to Benzoates	
		% cons	g/day	(mg/day)[1]	mg/kg bw/day (% ADI)[2]
Total Population					
14.1.2.1 Fruit Juice	Juices	39.8	145.0	36.3	0.57
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Refreshments, juice powder reconstituted				

Table 6.3.2.1-1 Reported Percent Consumption and General Population Consumption of Beverage Categories and Calculated Exposure to Benzoates by the Total Population and Split by Gender (POF 2008-2009) - Brand-Loyal Assessment

GSFA Food Category	POF Food Category	Reported Food Category Intakes		Calculated Exposure to Benzoates	
		% cons	g/day	(mg/day)[1]	mg/kg bw/day (% ADI)[2]
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Soft drinks	23.0	94.7	7.8	0.12
	Soft drinks (diet/light)	1.6	5.5	1.0	0.02
	Other nonalcoholic beverages[3]	0.8	2.7	0.2	<0.01
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Coffee	79.0	215.1	0	0
	Tea	6.0	31.3	0	0
Total mean *per capita* intakes[4]				**45.3**	**0.71 (14.3%)**
Males					
14.1.2.1 Fruit Juice	Juices	38.8	151.8	38.0	0.56
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Refreshments, juice powder reconstituted				
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Soft drinks	24.8	112.2	9.3	0.14
	Soft drinks (diet/light)	1.3	5.2	1.0	0.01
	Other nonalcoholic beverages[3]	1.0	3.2	0.3	<0.01
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Coffee	78.7	222.3	0	0
	Tea	4.3	26.8	0	0
Total mean *per capita* intakes (male)[4]				**48.4**	**0.71 (14.3%)**
Females					
14.1.2.1 Fruit Juice	Juices/refreshments/ juice powder reconstituted	40.7	138.7	34.7	0.58
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					

Table 6.3.2.1-1 Reported Percent Consumption and General Population Consumption of Beverage Categories and Calculated Exposure to Benzoates by the Total Population and Split by Gender (POF 2008-2009) - Brand-Loyal Assessment

GSFA Food Category	POF Food Category	Reported Food Category Intakes		Calculated Exposure to Benzoates	
		% cons	g/day	(mg/day)[1]	mg/kg bw/day (% ADI)[2]
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Refreshments, juice powder reconstituted				
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Soft drinks	21.2	78.4	6.5	0.11
	Soft drinks (diet/light)	1.8	5.8	1.1	0.02
	Other nonalcoholic beverages[3]	0.7	2.2	0.2	<0.01
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Coffee	79.3	208.4	0	0
	Tea	7.6	35.5	0	0
Total mean *per capita* intakes (female)[4]				**42.4**	**0.71 (14.3%)**

% cons = percent consumption of food category; ADI = acceptable daily intake; GSFA = Codex General Standard for Food Additives; POF = Pesquisa de Orçamentos Familiares (Household Budget Survey).
[1] Calculated as: [reported consumption] x [maximum or weighted average reported use level per food category]. See Table 6.2-1 for concentrations utilized.
[2] See Appendix F for calculation of weighted mean body weight per age group (63.6 kg for total population; 67.9 kg for males and 59.5 kg for females).
[3] The use level applied to the "Other non-alcoholic beverage" POF category was an average weighted value considering all beverage categories not otherwise considered, *i.e.*, energy drinks, sports drinks, RTD teas and RTD coffees.
[4] Calculated as: the sum of individual intakes calculated for each POF food category.

When the exposure estimates were determined according to age group, namely teenagers (ages 10 to 18 years), adults (ages 19 to 59 years), and elderly adults (ages 60 years and older), the highest estimated cumulative mean exposure to benzoates were identified in teenagers on a body weight basis, at 0.95 mg/kg body weight/day (19.1% ADI), which remained a very small fraction of the ADI even when considering the maximum benzoate use level of 250 ppm for the main contributing beverage category in addition to weighted average levels for all other beverage types. The mean general population intake amount adults and elderly were estimated to be 0.68 mg/kg body weight/day (13.7% ADI) and 0.44 mg/kg body weight/day (8.9% ADI), respectively (Table 6.3.2.1-2).

Table 6.3.2.1-2 Reported Percent Consumption and Average *Per capita* Consumption of Beverage Categories and Calculated Benzoate Intakes by Teenagers, Adults, and Elderly Adults (POF 2008-2009) - Brand-Loyal Assessment

GSFA Food Category	POF Food Category	Reported Food Category Intakes		Calculated Benzoate Intakes	
		% cons	g/day	(mg/day)[1]	mg/kg bw/day (% ADI)[2]
Teenagers					
14.1.2.1 Fruit Juice	Juices	43.7	167.8	42.0	0.75
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Refreshments, juice powder reconstituted				
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Soft drinks	28.2	123.7	10.2	0.18
	Soft drinks (diet/light)	1.2	4.1	0.8	0.01
	Other nonalcoholic beverages[3]	0.5	1.5	0.1	<0.01
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Coffee	62.8	166.7	0	0
	Tea	3.4	10.4	0	0
Total mean general population intakes (teenagers)				**53.1**	**0.95 (19.1%)**
Adults					
14.1.2.1 Fruit Juice	Juices	40.3	147.4	36.9	0.54
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Refreshments, juice powder reconstituted				
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Soft drinks	23.7	98.2	8.1	0.12
	Soft drinks (diet/light)	1.7	6.3	1.2	0.02
	Other nonalcoholic beverages[3]	1.2	3.0	0.2	<0.01
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Coffee	82.2	222.8	0	0
	Tea	5.9	34.4	0	0

Table 6.3.2.1-2 Reported Percent Consumption and Average *Per capita* Consumption of Beverage Categories and Calculated Benzoate Intakes by Teenagers, Adults, and Elderly Adults (POF 2008-2009) - Brand-Loyal Assessment

GSFA Food Category	POF Food Category	Reported Food Category Intakes		Calculated Benzoate Intakes	
		% cons	g/day	(mg/day)[1]	mg/kg bw/day (% ADI)[2]
Total mean general population intakes (adults)				**46.4**	**0.68 (13.7%)**
Elderly					
14.1.2.1 Fruit Juice	Juices	31.3	100.2	25.1	0.38
14.1.2.3 Concentrates for Fruit Juice					
14.1.3.1 Fruit Nectar					
14.1.3.3 Concentrates for Fruit Nectar					
14.1.3.4 Concentrates for Vegetable Nectars					
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Refreshments, juice powder reconstituted				
14.1.4 Water-based Flavored Drinks, including "sport", "energy", or "electrolyte" drinks and particulated drinks	Soft drinks	11.4	35.1	2.9	0.04
	Soft drinks (diet/light)	1.4	3.8	0.7	0.01
	Other nonalcoholic beverages[3]	1.2	3.0	0.2	<0.01
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	Coffee	86.6	246.9	0	0
	Tea	10.0	46.0	0	0
Total mean general population intakes (elderly)				**28.9**	**0.44 (8.9%)**

% cons = percent consumption of food category; ADI = acceptable daily intake; GSFA = General Standard for Food Additives; POF = Pesquisa de Orçamentos Familiares (Household Budget Survey).
[1] Calculated as: [reported consumption] x [maximum or weighted average benzoate use level per food category]. See Table 6.2-1 for concentrations utilized.
[2] See Appendix F for calculation of weighted mean body weight per age group (55.63 kg for teenagers; 67.83 kg for adults; and 65.11 kg for the elderly).
[3] The use level applied to the "Other nonalcoholic beverages" POF category was an average weighted value considering all beverage categories not otherwise considered, *i.e.*, energy drinks, sports drinks, RTD teas and RTD coffees.
[4] Calculated as: the sum of individual intakes calculated for each POF food category.

6.4 Conclusions on Brazilian Intakes

This exposure assessment estimated intakes of benzoates among the Brazilian population, calculated from reported benzoate use level data and summary statistics from the POF 2008-2009 for individual beverage categories. A conservative approach was taken in the selection of maximum levels (*i.e.*, Codex adopted interim ML of 250 ppm) for the deterministic

evaluations. A fixed concentration was required for the consumption figure representing a large aggregate of beverage types (*i.e.* "juices, refreshments, and juice powder reconstituted"), of which only a very small portion would be expected to contain benzoates. In the maximum deterministic scenario (Model 1), all beverage categories which may contain benzoates were assigned a concentration of 250 ppm (*i.e.* all POF beverage categories with the exception of coffee and tea). It is noted that the large share of the Brazilian beverage market does not contain benzoates (see Figure 6.2-1); however, due to the limitations of the POF food consumption data (wherein the consumption categories are very aggregated) and the availability of only general population intakes, it was considered appropriate to take a conservative approach to capture all potential benzoate-containing beverage products that may be represented by a POF beverage category. This is particularly notable for fruit juices (and concentrates) and nectars (and their concentrates) with a reported use of benzoates was "0". However, given the nature of the broader POF food category, namely "juices, refreshments, juice powder reconstituted", the use levels for 'fruit-juice based drinks' and 'non-carbonated water based flavoured drinks'- capped at 250 ppm per the Codex adopted interim levels - were therefore applied to this POF category. This will result in an overestimate of the intakes, as a proportion of the consumed volume (*i.e.*, those related to fruit juices and nectars) will not contain benzoates. This approach was carried over in both the maximum use level model (Model 1) and the brand-loyal model (Model 2) as this large beverage aggregate - with the potential to contribute highest to benzoate intakes - was selected as the brand loyal category.

Following on the reporting format available for beverage consumption in the POF, results are presented in terms of mean exposure for the general population for the entire cohort and by age and gender as well as 90th percentile intakes for males and females (heavy consumption statistics broken down by age brackets are not available). When considering exposure to beverages containing a maximum benzoate concentration of 250 ppm across all beverages, with the exception of coffees and teas (Model 1), the total mean general population intakes of benzoates within the total group surveyed (10 years+) was determined to be 0.97 mg/kg body weight/day (19.5% ADI). Mean and 90th percentile intakes were presented for males and females (90th percentile intakes only calculated considering 'Soft Drinks'). Among males these were 1.0 mg/kg body weight/day (20.1% ADI) and 1.07 mg/kg body weight/day (21.4% ADI), respectively. Among females, the mean and 90th percentile intakes were 0.95 mg/kg body weight/day; 18.9% ADI) and 0.93 mg/kg body weight/day; 18.7% ADI), respectively. The differences in beverage categorization and reporting of the mean and 90th percentile beverage consumption data within the POF report resulted in mean and heavy percentile estimates that are almost identical, as illustrated here. This in fact is an artifact of the presentation of the beverage consumption data publicly available in Brazil. That is, the mean and 90th percentile consumption estimates, while based on the same survey, are prepared independently of one another. The mean benzoate exposure levels are based on a summation of mean values for a number of beverage categories (*i.e.*, "refreshments, juice powder, reconstituted", "soft drinks",

"soft drinks (diet/light), "other nonalcoholic beverages") and the corresponding use levels, whereas the 90th percentile values were calculated based on intakes of "soft drinks" alone. Empirical evidence indicates that, in general, 95th percentiles of consumption can be estimated at approximately 3 times the mean (WHO, 1985). On this basis, considering the *Deterministic Maximum* model (Model 1) and a proxy for heavy-level consumption to complement the 90th percentile figure from the POF, the 95th percentile may be considered to be 2.91[17] mg/kg body weight/day (58.2% ADI) among all ages, 3.00 mg/kg body weight/day (60.0% ADI) in males, and 2.85 mg/kg body weight/day (57.0% ADI) in females. Among individual age groups, the highest mean general population intake of benzoates on a body weight basis was estimated at 1.34 mg/kg body weight/day (26.7% ADI) among teenagers. The mean general population intakes of benzoates in the remaining age groups (*i.e.*, adults and elderly adults) were determined to be 0.94 and 0.55 mg/kg body weight/day (18.8 and 10.9% ADI), respectively. No heavy-level consumption data were available by age group in the POF summary statistics. Using the same proxy as above, the 95th percentile of benzoate intake among teenagers, adults, and elderly adults may be estimated at 4.02 mg/kg body weight/day (80.4% ADI), 2.82 mg/kg body weight/day (56.4% ADI), and 1.65 mg/kg body weight/day (33.0% ADI), respectively. No exceedances of the ADI were identified when using this proxy for 95th percentiles of consumption at the maximum anticipated benzoate inclusion levels (based on the Codex adopted interim ML of 250 ppm).

When the assessment was adjusted to consider the mean intake values for all beverage categories, except the 'juices/refreshments/juice powder reconstituted' (which was the highest consumed beverage category in Brazil), *i.e.*, Model 2, the mean exposure level was calculated to be 0.71 mg/kg body weight/day (14.3% ADI) for all individuals and when split by gender. When the exposure estimates were determined according to age group, the highest estimated cumulative mean exposure to benzoates were identified in teenagers on a body weight basis, at 0.95 mg/kg body weight/day (19.1% ADI). The mean general population intake amount adults and elderly were estimated to be 0.68 mg/kg body weight/day (13.7% ADI) and 0.44 mg/kg body weight/day (8.9% ADI), respectively (Table 6.3.1.1-2). As mentioned previously, it was not possible to determine heavy- level intakes at the 95th percentile specifically for brand-loyal individuals based on the availability of summary statistics for "soft drinks" alone. Thus, the aforementioned approach is used as a proxy for heavy-level intakes within different age brackets resulting in theoretical intakes of 2.13 mg/kg body weight/day (42.6% ADI) for the total population; when split according to age group, estimated exposures to benzoate were calculated to be 2.85 mg/kg body weight/day (57.0% ADI) for teenagers, 2.04 mg/kg body weight/day (40.8% ADI) for adults, and 1.32 mg/kg body weight/day (26.4% ADI) for elderly.

In summary, based on the estimated benzoate intakes from beverages - calculated from maximum usage level data and food consumption data from the Brazilian POF (2008-2009), *i.e.*,

[17] Example: Calculated as 0.97 mg/kg body weight/day x 3 = 2.91 mg/kg body weight/day.

Model 1 - mean intakes for the total population, teenagers, adults and elderly were below the ADI for this additive. The estimated intakes at the mean and heavy-level (90th percentile) do not exceed 27% of the ADI based on data from the POF; or 80.4% of the ADI for this population group when a proxy ratio of 3-fold between the mean and 95th percentile was utilized. When industry-reported benzoate use levels were taken into account (*i.e.*, market-weighted average benzoate concentration), but still considering potential brand loyalty (for "juices/refreshments/juice powder reconstituted"), *i.e.*, Model 2, the 95th percentile intakes were slightly decreased across all population groups, with the highest exposure level calculated at 57% of the ADI. It is important to note that these calculations do not relate to toddlers and children (1 to 7 years), who typically have higher intakes on a body weight basis than other population groups (EFSA, 2011b). Furthermore, the results presented by the IBGE do not consider consumers only. Intakes by beverage consumers are likely to be slightly higher than the values presented herein. However, this assessment can be considered a conservative estimate of intakes as all non-alcoholic beverages permitted to contain benzoates were included in the assessments of intake, with no account for actual occurrence levels in these products.

7.0 OVERALL CONCLUSIONS

In the interest of refining the exposure estimate for benzoates, building on the 2014 industry-submitted data and the 2015 JECFA evaluation, the ICBA commissioned an updated intake assessment for four jurisdictions believed to be "worst-case" scenario jurisdictions relative to benzoate dietary exposure that would help identify the ceiling for safe benzoate uses in beverages globally. The refined intake assessment incorporated updated benzoate use level data and more realistic models for estimating dietary intake by incorporating factors to account for the "representativeness" of reported benzoate uses, based on market share. Realistic estimates of exposure are essential to enabling effective risk management decisions and contributing to transparent risk communication. Moreover, refining the JECFA conservative intake estimate is a notion fully endorsed by the WHO's Principles and methods for the risk assessment of chemicals in food (WHO, 2009). Specifically, it states:

> "Refinements could include more defined information about the foods that are consumed (**less conservative assumptions about the amounts consumed, the concentrations of the chemical in the foods,** impact of processing and food preparation, etc.), **or more complex exposure assessment models can be employed that allow more realistic simulation of consumer practices**." (**emphasis added** - see *Section 6.3.5 Refined dietary exposure assessments (probabilistic distributional analyses)* and Figure 6.1, EHC 240, reproduced below)

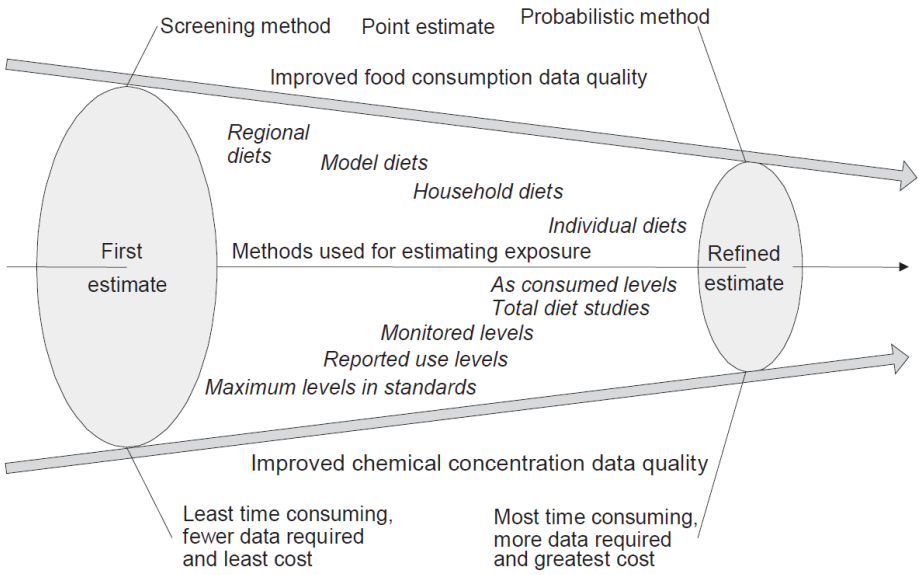


Fig. 6.1. Stepwise approach to obtaining realistic dietary exposure assessments

Importantly, the assessment conducted by JECFA in 2015 used summary statistics for consumption data for specific beverage categories available in the CIFOCOss database to evaluate exposure to benzoates. As previously mentioned, while the CIFOCOss database is a valuable screening tool for producing deterministic estimates of dietary exposures to certain substances, a more sophisticated model incorporating more complex considerations such as market share and brand loyalty may be warranted to render more accurate and relevant estimates of intake for a food additive (*e.g.*, benzoates which have a wide range of reported use levels within the specific subclasses of GSFA food category 14.1.4). Furthermore, as described in Section 2.2, the 2014-submitted assessment utilized maximum, as opposed to average, reported use levels, which was deemed by JECFA to be unsuitable.

Country-specific benzoate use levels (on a benzoic acid basis) were collected from all ICBA members for the U.S., Canada, Mexico and Brazil, specifically for those brands collectively contributing over 80% of the market share (in most instances) for each beverage type (*e.g.*, regular carbonated soft drinks). These jurisdictions – the "worst-case" scenario jurisdictions – were selected primarily based on national standards set higher than 400 ppm and for which a significant market disruption was anticipated based on ICBA first circular comments (using the Codex adopted interim ML of 250 ppm established by the CCFA48 as the threshold). ICBA members were requested to submit benzoate use level information based on all GSFA beverage categories to which benzoates are permitted for use (including 100% fruit juices) according to market share, with special emphasis on category *14.1.4 Water-based flavored drinks*, which was further organized into general subcategories:

- 14.1.2.1 Fruit Juice
- 14.1.2.3 Concentrates for Fruit Juice
- 14.1.3.1 Fruit Nectar
- 14.1.3.1 Concentrates for Fruit Nectar
- 14.1.3.4 Concentrates for Vegetable Nectars
- 14.1.4 Water-Based Flavored Drinks [further divided into general subcategories:]
    - Regular carbonated soft drinks
    - Diet carbonated soft drinks
    - Flavored water drinks
    - Fruit juice-based drinks
    - Energy drinks
    - Sports drinks
    - Ready-to-drink (RTD) teas
    - RTD coffees
- 14.1.5 Coffee, Coffee Substitutes, Tea, Herbal Infusions, and Other Hot Cereal and Grain Beverages, Excluding Cocoa

The most recent benzoate use level data collection indicated that, in general, benzoates were not broadly used in fruit juices (and concentrates thereof), fruit and vegetable nectars (and concentrates thereof), or coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages (as defined in GSFA 14.1.5) across these jurisdictions. Furthermore, market share data were received for these countries, detailing the volume in millions of gallons for top-selling beverage brands in the non-alcoholic beverage sector (to include those making up in most cases over 80% of the market share for each beverage type identified above under GSFA 14.1.4). Market share data also demonstrated that the majority of the overall liquid refreshment beverage market did not contain benzoates (benzoate-containing products were reported to penetrate 27.8% of the U.S. market; 21.0% in the Canadian market; 35.0% of the Brazilian market; and 15.0% of the Mexican market; see individual Sections for this information).

New dietary exposure estimates were generated from refined intake models, taking into account market share information and brand loyalty, two concepts that were previously not integrated into either industry's 2014 benzoate intake estimates or JECFA's 2015 assessment. A tiered approach to exposure assessments is recommended to maximize limited resources (WHO, 1985, 2009). As such, the current series of assessments may be considered a second 'tier' of exposure models for benzoates for 'high impact' regions based on actual industry reported use levels, providing more realistic intake estimates to the more conservative approaches undertaken in 2014 and 2015. Both probabilistic and distributional modeling were applied in most cases when the beverage consumption data was available (*e.g.,* individual level consumption data). Probabilistic modelling accounts for variability in the benzoate use level, including presence probability based on market share information. Distributional models

account for brand-loyalty among heavily consumed beverage types and market-weighted average concentrations for other categories. The details of these models are summarized in the points below:

- In the probabilistic models, all reported use levels (including those above the Codex adopted interim ML of 250 ppm), including non-occurrences, were incorporated into the model with a specific probability of being consumed that directly mirrored the market share of the beverage product.

- In the brand-loyal models, the scenario in which a consumer with specific beverage preferences may be a habitual consumer of one product line was analyzed. Although products with benzoate occurrences represent a relatively low portion of the overall market (see Figures 3.2-1, 4.2-1, 5.2-1, and 6.2-1), this model assumes the worst case in which an individual is loyal to a product containing the highest reported benzoate use. The remaining beverage categories were assumed to contain a market-weighted mean[18] concentration of benzoates. For all markets except Brazil, the largest contributing beverage category was regular carbonated soft drinks. Due to the atypical aggregation of beverage categories in Brazil, the largest contributing beverage category was "refreshments" (the "juices/refreshments/juice powder reconstituted" aggregate). In consideration of the Codex adopted interim maximum level of 250 ppm for beverages of pH ≤3.5 (and the proposed 500 ppm for beverages of pH >3.5), a restriction was placed on the brand-loyal category for those products below pH 3.5 so as to not exceed these levels (*i.e.*, for regular carbonated soft drinks in all jurisdictions and for "juices/refreshments/juice powder reconstituted" in Brazil); no such restriction was placed on beverages with a pH >3.5, as no reported use levels exceeded the limit of 500 ppm.

In the U.S., beverage consumption data from NHANES were retrieved and food codes were matched as closely as possible to the GSFA categories. Beverages that fall within GSFA category 14.1.4 had reported benzoate use levels which ranged from 0 to 430.5 ppm. In the probabilistic model (Model 1), *all* reported individual benzoate concentration data points were incorporated into the exposure model, and were matched with a presence probability that directly reflected the market share of that product. The general population groups had a mean and 95th percentile intake of 0.5 and 2.2 mg/kg body weight/day among all ages (10.3 and 44.2% ADI), respectively. In consumers only, the mean and 95th percentiles of intake among all ages across age groups were similar, at 0.5 and 2.3 mg/kg body weight/day (10.7 and 45.6% ADI), respectively. The highest intakes on a body weight basis were identified in adults, with a reported mean and 95th percentile intake of 0.6 and 2.3 mg/kg body weight/day, respectively; the heavy-level (95th percentile) estimates did not exceed 46.9% of the ADI. In the brand-loyal

[18] The market-weighted mean is an average concentration of benzoate use, weighted according to market share.

model (Model 2), a fixed concentration for regular carbonated soft drinks was established, with a 100% presence probability assumed. The highest benzoate use was set at 428.3 ppm (for cream sodas and root beers assumed to have a pH >3.5) and 250 ppm (for all remaining regular carbonated soft drinks with pH≤3.5); the market weighted mean was applied to all other categories. The mean and 95th percentiles of intake in the general population for all ages was estimated to be 0.9 and 3.3 mg/kg body weight/day (17.3 and 65.6% ADI), respectively. Among consumers only in this scenario, again the mean and 95th percentiles of intake were similar at 0.9 and 3.4 mg/kg body weight/day (18.1 and 67.6% ADI). Among the age brackets, the highest estimates for the mean were identified in other children and adolescents (age 8 to 17 years) at 1.0 mg/kg body weight/day (19.7% ADI), and at the heavy-level 95th percentile, the highest estimate was identified in toddlers and young children at 4.1 mg/kg body weight/day, equivalent to 82.4% of the ADI[19]. These estimates suggest that even in the worst-case in which a toddler or child is brand-loyal to a product line containing the maximum reported levels of benzoates among beverages with pH<3.5 and is chronically consuming this beverage, the cumulative exposure is not expected to result in intakes exceeding the ADI. All of the above suggest that the extreme outliers among toddlers/children using the most conservative assumptions do not have an estimated daily intake that is cause for concern.

In Canada, the same models were employed as above, whilst using country-specific benzoate use level data and branded-beverage market share information; however, due to the lack of publicly available food consumption data in this region, the NHANES dataset from the U.S. was used as a surrogate source of dietary information for Canada. As with the U.S. market, benzoates were reported to not be used in GSFA food categories corresponding to fruit juice (and concentrates), fruit and vegetable nectar (and concentrates) and coffee drinks. Within the subcategories of GSFA 14.1.4, the use levels ranged from 0 to 438 ppm. In the probabilistic model (Model 1), both the general population and consumer only mean and 95th percentile intakes were estimated to be 0.4 and 1.7 mg/kg body weight/day among all ages (7.4 to 7.7% and 34.5 to 35.0% ADI), respectively. Within the consumer only dataset, the highest mean and 95th percentile intakes were identified in adults, at 0.4 and 1.8 mg/kg body weight/day, respectively; heavy-level (95th percentile) intake was equivalent to 36.2% of the ADI for this population group. In the brand-loyal model (Model 2), consumers of regular carbonated soft drinks were assumed to be exposed broadly to both the maximum benzoate concentration of 438 ppm (for beverages such as cream sodas and root beers with pH>3.5) and 250 ppm based on the Codex adopted interim level (remaining regular carbonated soft drinks); the market weighted mean was applied to all other categories. Under this assumption, the general population was estimated to have intakes of benzoates at the mean and 95th percentile level of 0.8 and 3.2 mg/kg body weight/day (16.8 and 64.4% ADI). On a consumer only basis, the total mean and 95th percentile intake among all ages was estimated to be 0.9 and 3.4 mg/kg body weight/day (17.6 and 67.2% ADI). The highest mean intake estimate was identified in other

[19] The ADI of 0 to 5 mg/kg bodyweight/day was assigned at the forty-sixth meeting of the CCFA (JECFA, 1997).

children (including adolescents) at 1.0 mg/kg body weight/day, and the highest heavy-level (95th percentile) intake estimate was identified in toddlers/young children of 4.1 mg/kg body weight/day (equivalent to 82.8% of the ADI).

Both aggregate (24-hour dietary recall) and individual-level (FFQ) food consumption data were available in Mexico, allowing for deterministic, probabilistic, and distributional models to be employed. For the 24-hour dietary recall data, a brand-loyal deterministic model (Model 1) leveraged the summary statistics on beverage consumption in Mexico published by Stern *et al.* (2014), combined with a use level of 250 ppm (interim ML adopted by Codex) for regular carbonated soft drinks (no food codes were available for and no use levels exceeding 250 ppm were reported for regular carbonated soft drinks of pH > 3.5), and the market-weighted averages of the remaining beverage categories were employed, again with the conservative assumption that individuals will be habitually consuming regular carbonated soft drinks with the highest benzoate use level (Model 1). For the FFQ data, the approach in establishing a probabilistic and brand-loyal distributional model was identical to that of the U.S. and Canada. Again, all individual reported benzoate use level data points were entered in the probabilistic model (Model 2) with a presence probability that directly reflected the market share of the branded beverage product. In the brand-loyal distributional model (Model 3), the FFQ data were combined with the benzoate use levels established in the brand-loyal model described for Model 1 above. In Mexico, reported benzoate use was "0" for the GSFA categories corresponding to fruit juices (and concentrates), fruit nectar (and concentrates), concentrates for vegetable nectars, and coffee, coffee substitutes, tea (as defined by GSFA 14.1.5). Among the GSFA category 14.1.4, the reported use levels ranged from 0 to 300 ppm[20]. In the brand-loyal deterministic model (Model 1), the estimated benzoate intake level among the general population was estimated to be 1.2 mg/kg body weight/day in children aged 1 to 19 years and 0.9 mg/kg body weight/day in adults aged 20 years and older (24.1 and 17.9% ADI). Due to a lack of total consumer-only beverage estimates from the published 24-hour recall data, the consumer-only intakes from the highest contributing beverage category, caloric soda, was summated with the general population intakes from the remaining beverage categories. This approach rendered an estimated benzoate intake of 2.4 mg/kg body weight/day in children aged 1 to 19 years (48% ADI) and 1.7 mg/kg body weight/day in adults aged 20 years and older (34% ADI). When considering the probabilistic model (Model 2), mean and 95th percentiles of intake in the general population and consumer only dataset were 0.5 and 2.5 mg/kg body weight/day (9.8 to 10.5, and 49.1 to 51.0% ADI), respectively, for all ages. Among the consumers only dataset, the highest mean and 95th percentile among the age categories was identified to be in toddlers/young children aged 1 to 7 years old, having a mean and 95th percentile intake of 0.9 and 3.7 mg/kg body weight/day, respectively. This heavy-level intake among this age group

[20] Consistent with the approaches in the other brand loyal models, the maximum benzoate use level for the regular carbonated soft drink subcategory was restricted to 250 ppm. None of the beverages making up the larger share of the Mexican market were reported to have pH >3.5 and therefore did not have to be factored into this assessment.

was equivalent to 74.2% of the ADI. In the brand-loyal distributional model (Model 3), the general population mean and 95th percentile benzoate intake was estimated at 1.2 and 4.3 mg/kg body weight/day (24.8 and 86.2% ADI), respectively, whereas in the consumer only dataset, this was estimated to be 1.3 and 4.4 mg/kg body weight/day (26.4 and 88.6% ADI), respectively. Among consuming toddlers/young children, the mean and 95th percentile intakes were estimated to be 1.7 and 5.3 mg/kg body weight/day; as such, heavy consumers were estimated to exceed the ADI by 0.3 mg/kg body weight/day (or 5.4%). No exceedance of the ADI were observed in other age groups (*i.e.*, older children, adolescents and adults), indicating that this pattern is not observed in older individuals. Those brand-loyal toddlers and young children slightly exceeding the ADI corresponds to 75 toddlers/children out of 1,678 toddlers/children surveyed (*i.e.*, 4.5%) and out of all 7,397 respondents surveyed (*i.e.*, 1%) in ENSANUT. Considering the assumptions built into the brand loyal model, *i.e.*, that these individuals are assumed to be habitual consumers of regular carbonated soft drinks containing the maximum amount of benzoates at 250 ppm and average consumers of all other non-alcoholic beverages at 100% presence probability[21], the slight excursion above the ADI is not considered to be a cause for concern .

Lastly, in Brazil, the absence of publicly available individual-level beverage consumption data resulted in the use of summary statistics reports generated from the POF Household Budget Survey. As the published data are fixed and only available on an aggregate level, a deterministic approach had to be taken in which a single benzoate concentration was applied to each beverage category included in the POF publication. Due to the presentation of the summary statistics, two models were developed - a maximum use deterministic model (applying a 250 ppm use level across all categories in which benzoates have reported use); and a brand-loyal deterministic model (applying a maximum benzoate use level to the highest consumed aggregated beverage category - “juices/refreshments/juice powder reconstituted” - and a market-weighted mean concentration for the remaining categories). None of the beverages that make up the larger share of the Brazil market was reported to have pH >3.5. Further, there were no food codes available in the POF which specifically corresponded with such products. Therefore, these use levels were not factored into this assessment. In Brazil, reported use levels of benzoates in relevant beverages within 14.1.4 GSFA category exceeded 250 ppm. Reported uses of “0” were submitted for the remaining GSFA beverage categories. Using the maximum use model (Model 1), cumulative intakes of benzoates across all beverage categories in the general population were far below the ADI. In the general population, the mean intake was estimated to be 0.97 mg/kg body weight/day (19.5% ADI) among all ages and genders. Among the strata available in the POF publication (*i.e.*, individuals 10 years and older), the highest mean intake was identified in teenagers, with an estimate of 1.34 mg/kg body

[21] In the Mexican market, benzoate-containing beverages only represent 15.0% market share of the entire liquid refreshment beverage market (Figure 5.2-1)

weight/day (equivalent to 26.7% of the ADI). When considering the 90th percentile estimates[22], the heavy-level consumption of beverages resulted in intakes of benzoates of no more than 1.07 mg/kg body weight/day (males) and 0.93 mg/kg body weight/day (females). At the highest estimate, exposures equivalent to only 21.4% of the ADI was attained. Noteworthy is that the 95th percentile beverage consumption figures are not available from the POF publication. Using a proxy for the 95th percentile consumption, a supplementary estimate of heavy-level consumption was calculated as 2.91 mg/kg body weight/day (58.2% ADI) among all ages, and up to 4.02 mg/kg body weight/day (80.4% ADI) in teenagers (identified as having the highest exposure within the strata examined). When considering the brand-loyal deterministic model (Model 2), the mean intakes among the general population were 0.71 mg/kg body weight/day (14.3% ADI) among all ages and genders combined, and when split into males and females. Among the strata available in the POF publication, the highest mean intake was identified in teenagers, with an estimate of 0.95 mg/kg body weight/day (equivalent to 19.1% of the ADI). Using a proxy for the 95th percentile consumption, a supplementary estimate of heavy-level consumption was calculated as 2.13 mg/kg body weight/day (42.6% ADI) for the total population (all age groups and genders), 2.85 mg/kg body weight/day (57.0% ADI) for teenagers, 2.04 mg/kg body weight/day (40.8% ADI) for adults, and 1.32 mg/kg body weight/day (26.4% ADI) for elderly.

As a general consideration, when interpreting additive intake data, as noted by JECFA and re-iterated in Renwick and Walker (1993): *"…Because in most cases, data are extrapolated from life-time animal studies, the ADI relates to life-time use and provides a margin of safety large enough for toxicologists not to be particularly concerned about short-term use at exposure levels exceeding the ADI, providing the average intake over longer periods does not exceed it (WHO, 1987)*" (emphasis added). This concept should be taken into account, especially when assessing potential exceedances observed at the 95th percentile intakes among toddlers and children, which represent heavy-level exposures at a certain life stage (1 to 7 years) and are not observed when considering mean estimates in older age groups (7+ years).

The intake estimates described herein are intended to build upon the assessment conducted and submitted by the ICBA in 2014 and JECFA's 2015 intake estimates to benzoates. Use levels have been updated and corrected and branded beverage market share data have been incorporated into the assessments. These models were designed to represent the realistic scenario with representative use level information based on the market landscape as applied to the probabilistic models and the worst-case brand-loyal consumer scenario at the 95th percentile to ensure a thorough review of the range of estimated daily intakes. This more refined assessment should be leveraged in any risk management decision. The strength of these approaches is the use of market share data to accurately and reliably distribute with appropriate weight the benzoate use level information across the beverage categories and subcategories.

[22] It is noted that 95th percentile beverage consumption figures are not available from the POF publication.

This approach differs from the assessments conducted by industry in 2014, and by JECFA in 2015, in which fixed concentrations (the maximum reported level in the 2014 assessment; and the average reported level in the 2015 assessment) were applied across the entire beverage category or use levels were given equal probability of being used within the assessment. The focus of this assessment has been primarily on individual-based data, where available, to provide individual consumption patterns of beverages, unlike JECFA's 2015 assessment in beverages which was based on CIFOCOss summary statistics. For all jurisdictions except Brazil, individual-based data were available to achieve this.

Based on the food consumption datasets utilized; the updated and corrected benzoate use levels; market share data received for the U.S., Canada, Brazil, and Mexico – the "highest impact" markets; and, the worst-worst-case brand-loyal toddler/children consumer at the 95th percentile, estimates for the intake of benzoates from non-alcoholic beverages do not present a safety concern under current conditions of use.

8.0 REFERENCES

CDC (2013). *National Health and Nutrition Examination Survey: Analytic guidelines, 1999–2010*. National Center for Health Statistics. Hyattsville, MD: Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). (Vital and Health Statistics. Series 2, Number 161; http://www.cdc.gov/nchs/data/series/sr_02/sr02_161.pdf, accessed October 30, 2016).

CDC (2015). *National Health and Nutrition Examination Survey (NHANES): 2011-2012*. Hyattsville, MD: Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). (http://wwwn.cdc.gov/nchs/nhanes/search/nhanes11_12.aspx; Page last updated: November 6, 2015, accessed October 31, 2016).

Codex Alimentarius Commission (2016). Benzoates (210-213). In: *Codex General Standard for Food Additives (GSFA) online database*. Updated up to the 39th Session of the Codex Alimentarius Commission (2016). Rome: Codex Alimentarius Commission (CAC). (GSFA, Codex STAN 192-1995; http://www.fao.org/gsfaonline/groups/details.html?id=162, accessed October 31, 2016).

Dazult Ltd. (2016). *DaDiet - the dietary intake evaluation tool [software]*. Straffan, County Kildare, Ireland: Dazult Ltd. (Version 16.05; http://dadiet.daanalysis.com, accessed October 31, 2016).

EFSA (2011a). Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment (Guidance of EFSA) (question no EFSA-Q-2010-01471, approved 24 February 2011 by the European Food Safety Authority). EFSA J. 9(3):2097 [34 pp.]. DOI:10.2903/j.efsa.2011.2097. (http://www.efsa.europa.eu/en/efsajournal/pub/2097, accessed October 31, 2016).

EFSA (2011b). Overview of the procedures currently used at EFSA for the assessment of dietary exposure to different chemical substances (question no EFSA-Q-2010-01143, adopted on 02 December 2011 by European Food Safety Authority). EFSA J. 9:2490 [33 pp.]. DOI:10.2903/j.efsa.2011.2490. (http://www.efsa.europa.eu/en/efsajournal/pub/2490.htm, accessed October 31, 2016).

IBGE (2014). *Consumer expenditure survey 2008-2009. Analysis of personal food consumption in Brazil*. Rio de Janeiro, Brasil: Instituto Brasileiro de Geografia e Estatística (IBGE). (http://www.ibge.gov.br/english/estatistica/populacao/condicaodevida/pof/2008_2009_analise_consumo/default.shtm, accessed October 31, 2016).

ILSI (2011). Probabilistic. In: *GUIDEA - Guidance for Dietary Intake Exposure Assessment*. Brussels, Belgium: ILSI Europe (International Life Sciences Institute). (http://www.ilsi-guidea.org/index.php/Probabilistic, accessed October 30, 2016).

INSP (2012a). *Encuesta Nacional de Salud y Nutricion (ENSANUT) 2011-2012*. Cuernavaca, México: Instituto Nacional de Salud Pública (ISNP). (http://ensanut.insp.mx/index.php#.VIp0oivF8cE, accessed October 31, 2016).

INSP (2012b). *Resultados nacionales*. Cuernavaca, México: Instituto Nacional de Salud Pública (ISNP). (http://ensanut.insp.mx/informes/ENSANUT2012ResultadosNacionales.pdf, accessed October 31, 2016).

JECFA (1997). 3.6. Miscellaneous substances. 3.6.1. Benzyl acetate, benzyl alcohol, benzaldehyde, benzoic acid and the benzoate salts [Benzaldehyde]. In: *Evaluation of certain food additives and contaminants*. 46th report of the Joint FAO/WHO Expert Committee on Food Additives, Feb. 5-16, 1996. Geneva. Geneva: World Health Organization (WHO); 41–3, 59. (WHO Technical Report Series, no 868; http://whqlibdoc.who.int/trs/WHO_TRS_868.pdf, Accessed October 31, 2016).

JECFA (2016). 3.1.1 Benzoates: dietary exposure assessment. In: *Evaluation of certain food additives and contaminants*. Eightieth report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), June 16-25, 2015, Rome. Rome: Food and Agriculture Organization of the United Nations (FAO) / Geneva: World Health Organization (WHO); 13–6, 105–6. (WHO Technical Report Series, no 995; http://apps.who.int/iris/bitstream/10665/204410/1/9789240695405_eng.pdf?ua=1, accessed October 31, 2016).

Kroes R, Müller D, Lambe J, Löwik MRH, van Klaveren J, Kleiner J et al. (2002). Assessment of intake from the diet. Food Chem Toxicol. 40(2/3):327–85.

Mundo-Rosas V, de la Cruz-Góngora V, Jiménez-Aguilar A, Shamah-Levy T (2014). Diversidad de la dieta y consumo de nutrimentos en niños de 24 a 59 meses de edad y su asociación con inseguridad alimentaria [Dietary diversity and nutrient intake in children 24 to 59 months old and their association with food insecurity]. Salud Publica Mex. 56(Suppl. 1):39–46.

POF (2010). *Pesquisa de Orçamentos Familiares 2008-2009. Antropometria e estado nutricional de crianças, adolescentes e adultos no Brasil*. Rio de Janeiro, Brasil: Ministério da Saúde, Ministério do Planejamento, Orçamento e Gestão, Instituto Brasileiro de Geografia e Estatística (IBGE). (http://loja.ibge.gov.br/pesquisa-de-orcamentos-familiares-2008-2009-antropometria-e-estado-nutricional-de-criancas-adolescentes-e-adultos-no-brasil.html, accessed October 31, 2016).

POF (2011). *Pesquisa de Orçamentos Familiares 2008-2009. Análise do consume alimentar pessoal no Brazil*. Rio de Janeiro, Brasil: Ministério da Saúde, Ministério do Planejamento, Orçamento e Gestão, Instituto Brasileiro de Geografia e Estatística (IBGE). (http://biblioteca.ibge.gov.br/visualizacao/livros/liv50063.pdf, accessed October 31, 2016).

Renwick AG, Walker R (1993). An analysis of the risk of exceeding the acceptable or tolerable daily intake. Regul Toxicol Pharmacol. 18(3):463-480.

Romero-Martínez M, Shamah-Levy T, Franco-Núñez A, Villalpando S, Cuevas-Nasu L, Gutiérrez JP et al. (2013). Encuesta Nacional de Salud y Nutrición 2012: diseño y cobertura [National Health and Nutrition Survey 2012: design and coverage]. Salud Publica Mex 55(Suppl. 2):S332–40.

Souza Ade M, Pereira RA, Yokoo EM, Levy RB, Sichieri R (2013). Most consumed foods in Brazil: National Dietary Survey 2008-2009. Revista de Saúde Pública. 47(Suppl. 1):190S-9S.

Stern D, Piernas C, Barquera S, Rivera JA, Popkin BM (2014). Caloric beverages were major sources of energy among children and adults in Mexico, 1999-2012. J Nutr. 144(6):949-56 (including suppl. Tables).

USDA (2000). *1994-1996, 1998 Continuing Survey of Food Intakes by Individuals (CSFII) and Diet and Health Knowledge Survey (DHKS)*. Riverdale, MD: U.S. Department of Agriculture (USDA). On CD-ROM, PB2000-500027.

USDA (2014). *What we eat in America: National Health and Nutrition Examination Survey (NHANES): 2011-2012*. Riverdale, MD: U.S. Department of Agriculture (USDA). (http://www.ars.usda.gov/Services/docs.htm?docid=13793#release; Last Modified: October 2, 2014, accessed October 31, 2016).

WHO (1985). *Guidelines for the study of dietary intakes of chemical contaminants*. Geneva: World Health Organization (WHO), Global Environmental Monitoring System (GEMS). (WHO Offset Publication no. 87, http://apps.who.int/iris/bitstream/10665/39255/1/WHO_OFFSET_87.pdf, accessed October 30, 2016).

WHO (1987). *Principles for the safety assessment of food additives and contaminants in food*. Geneva: World Health Organization (WHO) / International Programme on Chemical Safety (IPCS) / United Nations Environment Programme (UNEP). (Environmental Health Criteria, no 70; http://www.inchem.org/documents/ehc/ehc/ehc70.htm, accessed October 30, 2016).

WHO (2009). Chapter 6: Dietary exposure assessment of chemicals in food. In: *Principles and methods for the risk assessment of chemicals in food*. Geneva: World Health Organization (WHO) / International Programme on Chemical Safety (IPCS). (Environmental Health Criteria, no 240; http://whqlibdoc.who.int/ehc/WHO_EHC_240_9_eng_Chapter6.pdf, Accessed October 31, 2016).

Appendix A
Supplementary Results of the United States Benzoate Intake Assessments

Appendix A.1 Probabilistic Model 1

Table A.1-1 Estimated Exposure to Benzoates from Individual Beverages Categories by Toddlers and Young Children (Ages 1 to 7 Years) Within the U.S. – Model 1 (2011-2012 NHANES Data) (number of individuals sampled = 1,241)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***0.36***	***2.10***	***0.39***	***2.13***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	11.2	<0.01	na	1.05	1.97
Energy Drinks	0	0	0	0	0
Flavored Water Drinks	5.7	0.02	na	0.09	0.87
Regular CSD	83.1	0.30	2.06	0.88	2.91
RTD Teas*	<0.1	na	na	na	na
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink; U.S. = United States.
* Indicates an intake estimates that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Table A.1-2 Estimated Exposure to Benzoates from Individual Beverages Categories by Other Children Including Adolescents (Ages 8 to 17 Years) Within the U.S. – Model 1 (2011-2012 NHANES Data) (number of individuals sampled = 1,468)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***0.45***	***1.99***	***0.47***	***2.01***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	12.5	0.06	0.37	0.64	1.82
Energy Drinks	0.3	<0.01*	na	0.19*	1.05*
Flavored Water Drinks	0.7	<0.01	na	0.02	na
Regular CSD	86.5	0.39	1.88	0.70	2.44
RTD Teas*	<0.1	na	na	na	na
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink; U.S. = United States

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Table A.1-3 Estimated Exposure to Benzoates from Individual Beverages Categories by Adults (Ages 18 Years and Older) Within the U.S. – Model 1 (2011-2012 NHANES Data) (number of individuals sampled = 4,506)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***0.55***	***2.30***	***0.57***	***2.34***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	45.3	0.25	1.52	1.18	3.53
Energy Drinks	1.0	0.01	na	0.58	1.00
Flavored Water Drinks	0.5	<0.01	na	0.03	na
Regular CSD	53.2	0.29	1.51	0.74	2.38
RTD Teas	<0.1	<0.01	na	0.09	0.57*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink; U.S. = United States.

Table A.1-4 Estimated Exposure to Benzoates from Individual Beverages Categories by the Total Population (All Ages) Within the U.S. – Model 1 (2011-2012 NHANES Data) (number of individuals sampled = 7,546)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***0.51***	***2.21***	***0.54***	***2.28***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	39.2	0.20	1.36	1.14	3.29
Energy Drinks	0.8	<0.01	na	0.53	1.00
Flavored Water Drinks	0.9	<0.01	na	0.04	na
Regular CSD	59.1	0.30	1.61	0.74	2.45
RTD Teas	<0.1	<0.01	na	0.05	0.55*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink; U.S. = United States.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Appendix A.2 Brand-Loyal Distributional Model 2

Table A.2-1 Estimated Exposure to Benzoates from Individual Beverages Categories by Toddlers and Young Children (Ages 1 to 7 Years) Within the U.S. – Model 2 (2011-2012 NHANES Data) (n = 1,241)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***0.74***	***4.04***	***0.80***	***4.12***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	4.8	0.04	na	0.93	1.74*
Energy Drinks	0	0	0	0	0
Flavored Water Drinks	1.1	0.01	0.05	0.04	0.08
Regular CSD	94.1	0.70	3.98	2.07	5.36
RTD Teas	<0.1	<0.01*	na	0.23*	0.22*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Table A.2-2 Estimated Exposure to Benzoates from Individual Beverages Categories by Other Children Including Adolescents (Ages 8 to 17 Years) Within the U.S. – Model 2 (2011-2012 NHANES Data) (n = 1,468)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***0.95***	***3.53***	***0.98***	***3.53***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	6.2	0.06	0.39*	0.67	1.56*
Energy Drinks	0.3	<0.01*	na	0.35*	0.63*
Flavored Water Drinks	0.4	<0.01	0.02	0.02	0.07
Regular CSD	92.7	0.88	3.46	1.58	4.27
RTD Teas	0.4	<0.01*	na	0.35*	0.35*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink; U.S. = United States.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Table A.2-3 Estimated Exposure to Benzoates from Individual Beverages Categories by Adults (Ages 18 Years and Older) Within the U.S. – Model 2 (2011-2012 NHANES Data) (n = 4,506)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***0.88***	***3.19***	***0.90***	***3.21***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	28.5	0.25	1.56	1.18	3.24
Energy Drinks	0.5	<0.01	na	0.43	0.80*
Flavored Water Drinks	0.2	<0.01	0.01	0.02	0.05
Regular CSD	70.7	0.62	2.76	1.57	4.48
RTD Teas	0.1	<0.01*	na	0.32*	0.508
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink; U.S. = United States.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Table A.2-4 Estimated Exposure to Benzoates from Individual Beverages Categories by the Total Population (All Ages) Within the U.S. – Model 2 (2011-2012 NHANES Data) (n = 7,546)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***0.87***	***3.28***	***0.90***	***3.38***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	23.4	0.20	1.31	1.14	3.17
Energy Drinks	0.4	<0.1	na	0.42	0.81*
Flavored Water Drinks	0.3	<0.01	0.02	0.02	0.06
Regular CSD	75.8	0.66	2.90	1.61	4.59
RTD Teas	0.1	<0.01*	na	0.33*	0.49*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink; U.S. = United States.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Appendix B
Representative NHANES Food Codes Selected for the United States and Canadian Intake Assessments

Representative 2011-2012 NHANES Food Codes Selected for the United States and Canadian Intake Assessments

14.1.2.1 Fruit Juice

11552200	Orange Julius
11553000	Fruit smoothie drink, made with fruit or fruit juice and dairy products
11553100	Fruit smoothie drink, NFS
61201020	Grapefruit juice, NS as to form
61201220	Grapefruit juice, canned, bottled or in a carton
61204000	Lemon juice, NS as to form
61204200	Lemon juice, canned or bottled
61204600	Lemon juice, frozen
61207000	Lime juice, NS as to form
61207200	Lime juice, canned or bottled
61210000	Orange juice, NFS
61210220	Orange juice, canned, bottled or in a carton
61210250	Orange juice, with calcium added, canned, bottled or in a carton
61213000	Tangerine juice, NFS
61213220	Tangerine juice, canned
61213800	Fruit juice blend, including citrus, 100% juice
61213900	Fruit juice blend, including citrus, 100% juice, with calcium added
63420100	Fruit juice bar, frozen, orange flavor
63420110	Fruit juice bar, frozen, flavor other than orange
63420200	Fruit juice bar, frozen, sweetened with low calorie sweetener, flavors other than orange
64100100	Fruit juice, NFS
64100110	Fruit juice blend, 100% juice
64100200	Fruit juice blend, with cranberry, 100% juice
64104010	Apple juice
64104600	Blackberry juice
64105400	Cranberry juice, 100%, not a blend
64116020	Grape juice
64120010	Papaya juice
64121000	Passion fruit juice
64124020	Pineapple juice
64126000	Pomegranate juice
64132010	Prune juice
64132500	Strawberry juice
64133100	Watermelon juice
64134000	Fruit smoothie drink, made with fruit or fruit juice only (no dairy products)
95342000	MonaVie acai blend beverage

Adjusted for a fruit juice content of 50%

92307500	Half and Half beverage, half iced tea and half fruit juice drink (lemonade)
92307510	Half and Half beverage, half iced tea and half fruit juice drink (lemonade), low calorie

14.1.2.3 Concentrates for Fruit Juice

61201620	Grapefruit juice, frozen (reconstituted with water)
61210620	Orange juice, frozen (reconstituted with water)
61210720	Orange juice, frozen, not reconstituted
61210820	Orange juice, frozen, with calcium added (reconstituted with water)
61213620	Tangerine juice, frozen (reconstituted with water)

14.1.3.1 Fruit Nectar

64200100	Fruit nectar, NFS
64201010	Apricot nectar
64202010	Cantaloupe nectar
64203020	Guava nectar
64204010	Mango nectar
64205010	Peach nectar
64210010	Papaya nectar
64213010	Passion fruit nectar
64215010	Pear nectar
64221010	Soursop (Guanabana) nectar

14.1.3.4 Concentrates for Vegetable Nectar

73105010	Carrot juice
74301100	Tomato juice
74301150	Tomato juice, low sodium
74303000	Tomato and vegetable juice, mostly tomato
74303100	Tomato and vegetable juice, mostly tomato, low sodium
74304000	Tomato juice with clam or beef juice
75132000	Mixed vegetable juice (vegetables other than tomato)
75132100	Celery juice
75200700	Aloe vera juice
78101000	Vegetable and fruit juice blend, 100% juice, with high vitamin C plus added vitamin E and vitamin A

14.1.4 Water-Based Flavored Drinks, Including “Sport”, “Energy”, or “Electrolyte” Drinks and Particulated Drinks

Diet Soft Drinks

92400100	Soft drink, NFS, sugar-free
92410315	Soft drink, cola type, reduced sugar
92410320	Soft drink, cola-type, sugar-free
92410350	Soft drink, cola-type, decaffeinated, sugar-free
92410370	Soft drink, pepper-type, sugar-free
92410400	Soft drink, pepper-type, decaffeinated, sugar-free
92410420	Cream soda, sugar-free
92410520	Soft drink, fruit-flavored, sugar free, caffeine free
92410560	Soft drink, fruit flavored, caffeine containing, sugar-free
92410620	Ginger ale, sugar-free
92410720	Root beer, sugar-free
92411610	Cola with fruit or vanilla flavor, sugar-free

Energy Drinks

92650000	Red Bull Energy Drink
92650005	Red Bull Energy Drink, sugar-free
92650200	Monster Energy Drink
92650205	Mountain Dew AMP Energy Drink
92650210	Mountain Dew AMP Energy Drink, sugar-free
92650700	Rockstar Energy Drink
92650705	Rockstar Energy Drink, sugar-free
92650800	Vault Energy Drink
92650805	Vault Zero Energy drink
92651000	Energy drink
95310200	Full Throttle Energy Drink
95310560	NOS Energy Drink
95310750	SoBe Energize Energy Juice Drink
95310800	Vault Energy Drink
95312400	Monster Energy Drink, Lo Carb
95312500	Mountain Dew AMP Energy Drink, sugar-free
95312550	No Fear Energy Drink, sugar-free
95312600	Red Bull Energy Drink, sugar-free
95312700	Rockstar Energy Drink, sugar-free
95312800	Vault Zero Energy Drink
95312900	XS Energy Drink

Flavored Water Drinks

92510650	Tamarind drink, Puerto Rican (Refresco de tamarindo)
92511010	Fruit flavored drink (formerly lemonade)
92530410	Fruit flavored drink, with high vitamin C
92541010	Fruit flavored drink, made from powdered mix
92542000	Fruit flavored drink, made from powdered mix, with high vitamin C
92550610	Fruit flavored drink, low calorie, with high vitamin C
92550620	Fruit flavored drink, low calorie
92552000	Fruit flavored drink, made from powdered mix, low calorie, with high vitamin C
92552010	Fruit flavored drink, made from powdered mix, low calorie
92560000	Fruit-flavored thirst quencher beverage
92416010	Mavi drink
94100300	Water, fruit flavored, sweetened, with high fructose corn syrup and low calorie sweetener
92410110	Carbonated water, sweetened
92410250	Carbonated water, sweetened, with low-calorie or no-calorie sweetener

Fruit Juice-Based Drinks

92431000	Carbonated juice drink, NS as to type of juice
92432000	Carbonated citrus juice drink
92433000	Carbonated noncitrus juice drink
92510610	Fruit juice drink
92510720	Fruit punch, made with fruit juice and soda
92510730	Fruit punch, made with soda, fruit juice, and sherbet or ice cream
92511250	Citrus fruit juice drink, containing 40-50% juice
92512050	Frozen daiquiri mix, from frozen concentrate, reconstituted
92512090	Pina Colada, nonalcoholic
92512110	Margarita mix, nonalcoholic
92513000	Fruit flavored frozen drink
92530510	Cranberry juice drink or cocktail, with high vitamin C
92530610	Fruit juice drink, with high vitamin C
92530950	Vegetable and fruit juice drink, with high vitamin C
92531030	Fruit juice drink, with thiamin (vitamin B1) and high vitamin C
92550030	Fruit juice drink, low calorie, with high vitamin C
92550040	Fruit juice drink, low calorie
92550110	Cranberry juice drink or cocktail, low calorie, with high vitamin C
92550350	Light orange juice beverage, 40-50% juice, lower sugar and calories, with artificial sweetener
92550400	Vegetable and fruit juice drink, low calorie, with high vitamin C
92550405	Vegetable and fruit juice drink, low calorie, with high vitamin C plus added vitamin E and vitamin A
92552020	Fruit juice drink, reduced sugar, with thiamin (vitamin B1) and high vitamin C
92552030	Fruit juice drink, reduced sugar, with vitamin E

92582100	Fruit juice drink, with high vitamin C, plus added calcium
92582110	Fruit juice drink, with thiamin (vitamin B1) and high vitamin C plus calcium
92582120	Fruit flavored drink, reduced sugar, with high vitamin C, plus added calcium
95341000	FUZE Slenderize fortified low calorie fruit juice beverage

Fruit-Flavored Concentrates and Mixes

92900100	Tang, dry concentrate*
92512040	Frozen daiquiri mix, frozen concentrate, not reconstituted*
92900110	Fruit-flavored beverage, dry concentrate, with sugar, not reconstituted*
92900200	Fruit-flavored beverage, dry concentrate, low calorie, not reconstituted*
92900300	Fruit-flavored thirst quencher beverage, dry concentrate, not reconstituted*

* Adjusted for not being reconstituted.

Ready-To-Drink Teas

Adjusted for a tea content of 50%

92307500	Half and Half beverage, half iced tea and half fruit juice drink (lemonade)
92307510	Half and Half beverage, half iced tea and half fruit juice drink (lemonade), low calorie

Regular Carbonated Soft Drinks

92400000	Soft drink, NFS
92410310	Soft drink, cola-type
92410330	Soft drink, cola-type, with higher caffeine
92410340	Soft drink, cola-type, decaffeinated
92410360	Soft drink, pepper-type
92410390	Soft drink, pepper-type, decaffeinated
92410410	Cream soda**
92410510	Soft drink, fruit-flavored, caffeine free
92410550	Soft drink, fruit flavored, caffeine containing
92410610	Ginger ale
92410710	Root beer**
92411510	Cola with fruit or vanilla flavor

** Further designated to have pH > 3.5.

Sports Drinks

92560100	Gatorade Thirst Quencher sports drink
92560200	Powerade sports drink
92565000	Fruit-flavored sports drink or thirst quencher beverage, low calorie
92565100	Gatorade G2 thirst quencher sports drink, low calorie
92565200	Powerade Zero sports drink, low calorie
92570100	Fluid replacement, electrolyte solution

95320200	Gatorade Thirst Quencher sports drink
95320500	Powerade sports drink
95322200	Gatorade G2 Thirst Quencher sports drink, low calorie
95323000	Fruit-flavored sports drink or thirst quencher beverage, low calorie
94210100	Propel Water
94210200	Glaceau Water
94210300	SoBe Lifewater
94220200	Glaceau Water, low calorie

14.1.5 Coffee, Coffee Substitutes, Tea, Herbal Infusions, and Other Hot Cereal and Grain Beverages, Excluding Cocoa

92101920	Blended coffee beverage, made with regular coffee, milk, and ice, sweetened
92101930	Blended coffee beverage, made with decaffeinated coffee, milk, and ice, sweetened
92100000	Coffee, NS as to type
92100500	Coffee, regular, NS as to ground or instant
92101000	Coffee, made from ground, regular
92101500	Coffee, made from ground, equal parts regular and decaffeinated
92101610	Coffee, espresso
92101630	Coffee, espresso, decaffeinated
92101700	Coffee, made from ground, regular, flavored
92101800	Coffee, Cuban
92101900	Coffee, latte
92101910	Coffee, latte, decaffeinated
92101950	Coffee, mocha
92101960	Coffee, mocha, made with soy milk
92103000	Coffee, made from powdered instant, regular
92104000	Coffee, made from powdered instant, 50% less caffeine
92105000	Coffee, liquid concentrate
92105010	Coffee, made from liquid concentrate
92111000	Coffee, decaffeinated, NS as to ground or instant
92111010	Coffee, decaffeinated, made from ground
92114000	Coffee, decaffeinated, made from powdered instant
92121000	Coffee, made from powdered instant mix, with whitener and sugar, instant
92121010	Coffee, made from powdered instant mix, presweetened, no whitener
92121020	Coffee and cocoa (mocha), made from powdered instant mix, with whitener, presweetened
92121030	Coffee and cocoa (mocha), made from powdered instant mix, with whitener and low calorie sweetener
92121050	Coffee and cocoa (mocha), made from powdered instant mix, with whitener and low calorie sweetener, decaffeinated
92121040	Coffee, made from powdered instant mix, with whitener and low calorie sweetener
92130000	Coffee, regular, presweetened with sugar, pre-lightened
92130001	Coffee, decaffeinated, presweetened with sugar, pre-lightened

92130005	Coffee, regular, with low-calorie sweetener, pre-lightened
92130006	Coffee, decaffeinated, with low-calorie sweetener, pre-lightened
92130020	Coffee, presweetened with sugar
92152000	Coffee and chicory, made from ground
92153100	Coffee, decaffeinated, with cereal
92161000	Cappuccino
92162000	Cappuccino, decaffeinated
92162005	Cappuccino, decaffeinated, sweetened
92191100	Coffee, dry instant powder, regular*
92191200	Coffee, dry instant powder, decaffeinated*
92191250	Coffee, dry, acid neutralized*
92192000	Coffee and cocoa (mocha) mix, dry instant powder with whitener, presweetened*
92193000	Coffee, dry instant powder, with whitener and sugar*
92193020	Coffee, dry instant powder, with whitener and low calorie sweetener*
92201010	Postum
92202010	Chicory
92203000	Cereal beverage
92203110	Cereal beverage with beet roots, from powdered instant
92205000	Rice beverage
92291300	Postum, dry powder*
92301000	Tea, NS as to type, unsweetened
92301060	Tea, NS as to type, presweetened with sugar
92301080	Tea, NS as to type, presweetened with low calorie sweetener
92301100	Tea, NS as to type, decaffeinated, unsweetened
92301130	Tea, NS as to type, presweetened, NS as to sweetener
92301160	Tea, NS as to type, decaffeinated, presweetened with sugar
92301180	Tea, NS as to type, decaffeinated, presweetened with low calorie sweetener
92301190	Tea, NS as to type, decaffeinated, presweetened, NS as to sweetener
92302000	Tea, leaf, unsweetened
92302200	Tea, leaf, presweetened with sugar
92302300	Tea, leaf, presweetened with low calorie sweetener
92302400	Tea, leaf, presweetened, NS as to sweetener
92302500	Tea, leaf, decaffeinated, unsweetened
92302600	Tea, leaf, decaffeinated, presweetened with sugar
92302700	Tea, leaf, decaffeinated, presweetened with low calorie sweetener
92302800	Tea, leaf, decaffeinated, presweetened, NS as to sweetener
92304000	Tea, made from frozen concentrate, unsweetened
92305000	Tea, made from powdered instant, presweetened, NS as to sweetener
92305010	Tea, made from powdered instant, unsweetened
92305040	Tea, made from powdered instant, presweetened with sugar
92305050	Tea, made from powdered instant, decaffeinated, presweetened with sugar
92305090	Tea, made from powdered instant, presweetened with low calorie sweetener

92305110	Tea, made from powdered instant, decaffeinated, presweetened with low calorie sweetener
92305180	Tea, made from powdered instant, decaffeinated, unsweetened
92305800	Tea, made from powdered instant, decaffeinated, presweetened, NS as to sweetener
92306000	Tea, herbal
92306020	Tea, herbal, presweetened with sugar
92306030	Tea, herbal, presweetened with low calorie sweetener
92306040	Tea, herbal, presweetened, NS as to sweetener
92306090	Tea, hibiscus
92306100	Corn beverage
92610010	Horchata beverage, made with almonds or other nuts and seeds
92611010	Oatmeal beverage, Puerto Rican
92611100	Oatmeal beverage with milk (Atole de avena)
92611510	Horchata beverage, made with rice
92611600	Horchata beverage, NFS
92613010	Atole (corn meal beverage)
92613510	Corn beverage with chocolate and milk (Champurrado, Atole de Chocolate)

* Adjusted for not being reconstituted.

Appendix C
Supplementary Results of the Canadian Benzoate Intake Assessments

Appendix C.1 Probabilistic Model 1

Table C.1-1 Estimated Exposure to Benzoates from Individual Beverages Categories by Toddlers and Young Children (Ages 1 to 7 Years) Within Canada – Model 1 (2011-2012 NHANES Surrogate Data) (number of individuals sampled = 1,241)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***0.23***	***1.63***	***0.24***	***1.63***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	13.2	0.03	na	0.79	1.81
Energy Drinks	0	0	0	0	0
Regular CSD	86.7	0.20	1.61	0.58	2.60
RTD Teas	0.1	<0.01*	na	0.32*	0.32*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Table C.1-2 Estimated Exposure to Benzoates from Individual Beverages Categories by Other Children Including Adolescents (Ages 8 to 17 Years) Within Canada – Model 1 (2011-2012 NHANES Surrogate Data) (number of individuals sampled = 1,468)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***0.32***	***1.68***	***0.34***	***1.77***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	15.3	0.05	0.34	0.56	1.41
Energy Drinks	0.6	<0.01*	na	0.28*	0.34*
Regular CSD	84.0	0.27	1.65	0.49	2.16
RTD Teas	<0.1	na	na	na	na
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Table C.1-3 Estimated Exposure to Benzoates from Individual Beverages Categories by Adults (Ages 18 Years and Older) Within Canada – Model 1 (2011-2012 NHANES Surrogate Data) (number of individuals sampled = 4,506)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***0.40***	***1.75***	***0.41***	***1.81***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	56.0	0.23	1.38	1.06	3.05
Energy Drinks	0.9	<0.01	na	0.37	1.58
Regular CSD	43.1	0.17	1.07	0.44	1.58
RTD Teas	0.1	<0.01	na	0.12	0.37*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Table C.1-4 Estimated Exposure to Benzoates from Individual Beverages Categories by the Total Population (All Ages) Within Canada – Model 1 (2011-2012 NHANES Surrogate Data) (number of individuals sampled = 7,546)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***0.37***	***1.72***	***0.39***	***1.75***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	48.8	0.18	1.22	1.02	2.97
Energy Drinks	0.8	<0.01	na	0.36	1.58
Regular CSD	50.4	0.19	1.13	0.46	1.75
RTD Teas	0.1	<0.01*	na	0.07*	0.37*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Appendix C.2 Brand-Loyal Distributional Model 2

Table C.2-1 Estimated Exposure to Benzoates from Individual Beverages Categories by Toddlers and Young Children (Ages 1 to 7 Years) Within Canada – Model 2 (2011-2012 NHANES Surrogate Data) (n = 1,241)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***0.73***	***4.04***	***0.79***	***4.14***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	4.3	0.03	na	0.83	1.54*
Energy Drinks	0	0	0	0	0
Regular CSD	95.77	0.70	3.98	2.08	5.36
RTD Teas	<0.1	<0.01*	na	0.19*	0.18*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Table C.2-2 Estimated Exposure to Benzoates from Individual Beverages Categories by Other Children Including Adolescents (Ages 8 to 17 Years) Within Canada – Model 2 (2011-2012 NHANES Surrogate Data) (n = 1,468)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***0.94***	***3.61***	***0.98***	***3.61***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	5.5	0.05	0.35*	0.59	1.38*
Energy Drinks	0.3	<0.01*	na	0.34*	0.62*
Regular CSD	93.9	0.88	3.46	1.58	4.30
RTD Teas	0.3	<0.01*	na	0.29*	0.29*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Table C.2-3 Estimated Exposure to Benzoates from Individual Beverages Categories by Adults (Ages 18 Years and Older) Within Canada – Model 2 (2011-2012 NHANES Surrogate Data) (n = 4,506)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***0.85***	***3.10***	***0.87***	***3.14***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	26.1	0.22	1.38	1.05	2.87
Energy Drinks	0.5	<0.01	na	0.42	0.78*
Regular CSD	73.3	0.62	2.76	1.58	4.48
RTD Teas	0.1	<0.01*	na	0.26*	0.42*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Table C.2-4 Estimated Exposure to Benzoates from Individual Beverages Categories by the Total Population (All Ages) Within Canada – Model 2 (2011-2012 NHANES Surrogate Data) (n = 7,546)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***0.84***	***3.22***	***0.88***	***3.36***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	21.3	0.18	1.16	1.01	2.80
Energy Drinks	0.4	<0.01	na	0.41	0.79*
Regular CSD	78.3	0.66	2.90	1.61	4.59
RTD Teas	0.1	<0.01*	na	0.27*	0.41*
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; na = not available; NHANES = National Health and Nutrition Examination Survey; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

Appendix D
Supplementary Results from the Mexican Benzoate Intake Assessments (Food Frequency Questionnaire)

Appendix D.1 Probabilistic Model 2

Table D.1-1 Estimated Exposure to Benzoates from Individual Beverages Categories by Toddlers and Young Children (Ages 1 to 7 Years) Within Mexico – Model 2 (2012 ENSANUT FFQ Data) (number individuals surveyed = 1,678)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***0.80***	***3.70***	***0.85***	***3.71***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	0.1	<0.01	na	0.20	0.36*
Energy Drinks[1]	na	na	na	na	na
Flavored Water Drinks	32.5	0.26	1.77	1.12	3.90
Fruit Juice-Based Drinks	47.8	0.38	2.22	1.00	3.70
Regular CSD	19.6	0.16	0.87	0.22	1.12
RTD Teas[2]	na	na	na	na	na
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; ENSANUT = Encuesta Nacional de Salud y Nutricion; FFQ = food frequency questionnaire; na = not available; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.
[1] No food codes representative for Energy Drinks were identified in the 2012 ENSANUT FFQ.
[2] No food codes representative for RTD Teas were identified in the 2012 ENSANUT FFQ.

Table D.1-2 Estimated Exposure to Benzoates from Individual Beverages Categories by Other Children Including Adolescents (Ages 8 to 17 Years) Within Mexico – Model 2 (2012 ENSANUT FFQ Data) (number individuals surveyed = 2,525)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***0.61***	***2.87***	***0.64***	***2.95***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	0.4	<0.01	na	0.45	1.81
Energy Drinks[1]	na	na	na	na	na
Flavored Water Drinks	37.7	0.23	1.40	0.90	3.32
Fruit Juice-Based Drinks	36.6	0.22	1.58	0.65	2.49
Regular CSD	25.3	0.15	0.92	0.20	1.22
RTD Teas[2]	na	na	na	na	na
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; ENSANUT = Encuesta Nacional de Salud y Nutricion; FFQ = food frequency questionnaire; na = not available; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.
[1] No food codes representative for Energy Drinks were identified in the 2012 ENSANUT FFQ.
[2] No food codes representative for RTD Teas were identified in the 2012 ENSANUT FFQ.

Table D.1-3 Estimated Exposure to Benzoates from Individual Beverages Categories by Adults (Ages 18 Years and Older) Within Mexico – Model 2 (2012 ENSANUT FFQ Data) (n = 3,194)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***0.38***	***1.99***	***0.41***	***2.07***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	4.5	0.02	na	0.55	2.23
Energy Drinks[1]	na	na	na	na	na
Flavored Water Drinks	23.3	0.09	0.65	0.69	2.20
Fruit Juice-Based Drinks	46.1	0.18	1.06	0.52	1.98
Regular CSD	26.0	0.10	0.69	0.14	0.88
RTD Teas[2]	na	na	na	na	na
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; ENSANUT = Encuesta Nacional de Salud y Nutricion; FFQ = food frequency questionnaire; na = not available; RTD = ready-to-drink.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

[1] No food codes representative for Energy Drinks were identified in the 2012 ENSANUT FFQ.

[2] No food codes representative for RTD Teas were identified in the 2012 ENSANUT FFQ.

Table D.1-4 Estimated Exposure to Benzoates from Individual Beverages Categories by Total Population (All Ages) Within Mexico – Model 2 (2012 ENSANUT FFQ Data) (n = 7,397)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***0.49***	***2.45***	***0.52***	***2.55***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	2.4	0.01	na	0.54	1.97
Energy Drinks[1]	na	na	na	na	na
Flavored Water Drinks	29.5	0.14	1.01	0.84	2.63
Fruit Juice-Based Drinks	43.7	0.21	1.31	0.62	2.48
Regular CSD	24.4	0.12	0.78	0.16	0.95
RTD Teas[2]	na	na	na	na	na
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; ENSANUT = Encuesta Nacional de Salud y Nutricion; FFQ = food frequency questionnaire; na = not available; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.
[1] No food codes representative for Energy Drinks were identified in the 2012 ENSANUT FFQ.
[2] No food codes representative for RTD Teas were identified in the 2012 ENSANUT FFQ.

Appendix D.2 Brand-Loyal Distributional Model 3

Table D.2-1 Estimated Exposure to Benzoates from Individual Beverages Categories by Toddlers and Young Children (Ages 1 to 7 Years) – Model 2 (2012 ENSANUT FFQ Data) (n = 1,678)

Food-Use Category	% Contribution to Total Mean Intake	General Population Exposure (mg/kg bw/day)		Consumers Only Exposure (mg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
All	***100***	***1.57***	***5.08***	***1.67***	***5.27***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	<0.1	<0.01*	na	0.21*	0.31*
Energy Drinks[1]	na	na	na	na	na
Flavored Water Drinks	17.0	0.27	1.75	1.15	3.57
Fruit Juice-Based Drinks	20.1	0.32	1.66	0.83	2.40
Regular CSD	62.8	0.99	4.00	1.36	4.53
RTD Teas[2]	na	na	na	na	na
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; ENSANUT = Encuesta Nacional de Salud y Nutricion; FFQ = food frequency questionnaire; na = not available; RTD = ready-to-drink.
* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.
[1] No food codes representative for Energy Drinks were identified in the 2012 ENSANUT FFQ.
[2] No food codes representative for RTD Teas were identified in the 2012 ENSANUT FFQ.

Table D.2-2 Estimated Exposure to Benzoates from Individual Beverages Categories by Other Children Including Adolescents (Ages 8 to 17 Years) – Model 3 (2012 ENSANUT FFQ Data) (n = 2,525)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***1.47***	***4.80***	***1.55***	***4.81***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	0.2	<0.01*	na	0.43*	1.51*
Energy Drinks[1]	na	na	na	na	na
Flavored Water Drinks	14.6	0.22	1.27	0.84	2.84
Fruit Juice-Based Drinks	13.7	0.20	1.24	0.59	1.74
Regular CSD	71.4	1.05	4.01	1.37	4.56
RTD Teas[2]	na	na	na	na	na
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; ENSANUT = Encuesta Nacional de Salud y Nutricion; FFQ = food frequency questionnaire; na = not available; RTD = ready-to-drink.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

[1] No food codes representative for Energy Drinks were identified in the 2012 ENSANUT FFQ.

[2] No food codes representative for RTD Teas were identified in the 2012 ENSANUT FFQ.

Table D.2-3 Estimated Exposure to Benzoates from Individual Beverages Categories by Adults (Ages 18 Years and Older) – Model 3 (2012 ENSANUT FFQ Data) (n = 3,194)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***1.08***	***3.80***	***1.16***	***3.97***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	1.7	0.02	na	0.57	2.33*
Energy Drinks[1]	na	na	na	na	na
Flavored Water Drinks	7.9	0.09	0.63	0.65	1.89
Fruit Juice-Based Drinks	14.1	0.15	0.82	0.44	1.42
Regular CSD	76.4	0.83	3.56	1.13	3.90
RTD Teas[2]	na	na	na	na	na
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; ENSANUT = Encuesta Nacional de Salud y Nutricion; FFQ = food frequency questionnaire; na = not available; RTD = ready-to-drink.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

[1] No food codes representative for Energy Drinks were identified in the 2012 ENSANUT FFQ.

[2] No food codes representative for RTD Teas were identified in the 2012 ENSANUT FFQ.

Table D.2-4 Estimated Exposure to Benzoates from Individual Beverages Categories by Total Population (All Ages) – Model 3 (2012 ENSANUT FFQ Data) (n = 7,397)					
Food-Use Category	**% Contribution to Total Mean Intake**	**General Population Exposure (mg/kg bw/day)**		**Consumers Only Exposure (mg/kg bw/day)**	
		Mean	**95th Percentile**	**Mean**	**95th Percentile**
All	***100***	***1.24***	***4.31***	***1.32***	***4.43***
14.1.2.1 Fruit Juice	0	0	0	0	0
14.1.2.3 Concentrates for Fruit Juice	0	0	0	0	0
14.1.3.1 Fruit Nectar	0	0	0	0	0
14.1.3.4 Concentrates for Vegetable Nectar	0	0	0	0	0
14.1.4 Water-based Flavored Drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks					
Diet CSD	1.0	0.01	na	0.55	2.09*
Energy Drinks[1]	na	na	na	na	na
Flavored Water Drinks	11.2	0.14	0.93	0.81	2.41
Fruit Juice-Based Drinks	14.9	0.19	1.04	0.53	1.67
Regular CSD	72.5	0.90	3.60	1.22	4.12
RTD Teas[2]	na	na	na	na	na
14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa	0	0	0	0	0

bw = body weight; CSD = carbonated soft drinks; ENSANUT = Encuesta Nacional de Salud y Nutricion; FFQ = food frequency questionnaire; na = not available; RTD = ready-to-drink.

* Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirement.

[1] No food codes representative of Energy Drinks were identified in the 2012 ENSANUT FFQ.

[2] No food codes representative of RTD Teas were identified in the 2012 ENSANUT FFQ.

Appendix E
Representative ENSANUT Food Codes Selected for the Mexican Intake Assessments

14.1.2.1 Fruit Juice

jugos naturales con azúcar
jugos naturales sin azúcar

14.1.3.1 Fruit Nectar

néctares de frutas o pulpa de frutas industrializados con az

14.1.3.4 Concentrates for Vegetable Juice

néctares de frutas o pulpa de frutas industrializados con az

14.1.4 Water-Based Flavored Beverages

refresco dieta
refresco normal
aguas de fruta natural con azúcar
aguas de fruta natural sin azúcar
bebidas o aguas de sabor industrializadas con azúcar
bebidas o aguas de sabor industrializadas sin azúcar

14.1.5 Coffee, coffee substitutes, tea, herbal infusions, and other hot cereal and grain beverages, excluding cocoa

té o infusión:-azúcar agregada al té
té o infusión:-té sin azúcar
café:-azúcar agregada al café
café:-café sin azúcar
café:-leche agregada al café (aparte de la reportada en p. l
café:-sustituto de crema agregada al café

Appendix F
Calculation of Weighted Body Weights per Age Group in POF 2008-2009

The median body weight was reported per age (years) from 10 years old to 75 years and over, as provided by POF (POF, 2010) (see Table F-1 below). In considering the number of individuals per age group, the reported body weight values were multiplied by the number of individuals sampled per age group, and then averaged between male and female genders in order to obtain a more accurate value of the average body weight per age group. These body weights are used to calculate the average *per capita* consumption on a per kilogram body weight basis, as discussed in Section 6.3 of the current report.

Table F-1 Reported Body Weight and Calculated Weighted Body Weight Values

Years	Sample N		Median Body Weight (kg)	
	Males	Females	Males	Females
Teenagers				
10 years	1,791	1,719	33.4	34.3
11 years	1,868	1,770	36.8	39.5
12 years	1,873	1,764	42.0	44.2
13 years	1,818	1,852	47.4	47.9
14 years	1,936	1,846	52.3	50.0
15 years	1,871	1,869	57.0	52.6
16 years	1,792	1,625	60.1	53.3
17 years	1,730	1,634	63.1	54.1
18 years	1,682	1,608	65.3	55.4
19 years	1,723	1,639	65.9	56.2
Total	**18,084**	**17,326**		
Weighted Average, By Gender, Teenagers			**52.1**	**36.7**
Overall Weighted Average, Teenagers			**50.4**	
Adults				
Years	**Sample N**		**Median Body Weight (kg)**	
	Males	**Females**	**Males**	**Females**
20 to 24 years	8,299	7,938	69.4	57.8
25 to 29 years	8,084	7,945	72.7	60.5
30 to 34 years	7,044	7,288	74.2	62.0
35 to 44 years	12,511	13,332	74.6	63.8
45 to 54 years	9,845	10,904	74.6	65.1
55 to 64 years	6,585	7,545	73.1	65.3
Total	**52,368**	**54,952**		
Weighted Average, by Gender, Adults			**73.2**	**62.7**
Overall Weighted Average, Adults			**67.8**	

Table F-1 Reported Body Weight and Calculated Weighted Body Weight Values				
Years	**Sample N**		**Median Body Weight (kg)**	
	Males	**Females**	**Males**	**Females**
Elderly Adults				
Years	**Sample N**		**Median Body Weight (kg)**	
	Males	**Females**	**Males**	**Females**
65 to 74 years	4,035	4,650	70.3	63.4
75 years up	2,229	2,847	66.8	59.2
Total	**6,264**	**7,497**		
Weighted Average, By Gender, Elderly Adults			**69.1**	**61.8**
Overall Weighted Average, Elderly Adults			**65.1**	
Weighted Average, Males Aged 10 to 75+			**67.9**	
Weighted Average, Females Aged 10 to 75+			**59.5**	
Weighted Average, Both Genders Aged 10 to 75+			**63.6**	

Appendix G
Representative Pesquisa de Orçamentos Familiares (POF) Food Codes for the Brazilian Benzoate Intake Assessments

Pesquisa de Orçamentos Familiares (POF) Food Codes Selected to Represent Beverage Categories for Brazilian Benzoate Intake Assessment Uses

Juices, Refreshments, and Juice powder reconstituted

	Sucos
8500401	Suco
8500402	Suco de abacaxi
8507902	Suco de abacaxi orgânico
8500403	Suco de acerola
8507903	Suco de acerola orgânico
8500404	Suco de beterraba
8213601	Suco de clorofila
8500405	Suco de cupuaçú
8500406	Suco de goiaba
8507906	Suco de goiaba orgânico
8500407	Suco de laranja
8500411	Suco de laranja cenoura e beterraba
8507911	Suco de laranja cenoura e beterraba orgânico
8500408	Suco de laranja com banana
8500409	Suco de laranja e beterraba
8500410	Suco de laranja e cenoura
8507907	Suco de laranja orgânico
8500412	Suco de mamão
8500413	Suco de manga
8507913	Suco de manga orgânico
8500414	Suco de maracujá
8507914	Suco de maracujá orgânico
8500415	Suco de melão
8500416	Suco de morango
8507916	Suco de morango orgânico
8500417	Suco de pêssego
8500418	Suco de pêssego em calda
8507918	Suco de pêssego em calda orgânico
8507917	Suco de pêssego orgânico
8507901	Suco orgânico
8302409	Cajuína
	Refrescos/sucos em pó reconstituído
8202402	Q-suco
8202403	Q-refresko
8500601	Refresco
8500602	Refresco de caju
8500603	Refresco de groselha
8500604	Refresco de laranja
8500605	Refresco de maracujá
8500606	Refresco de limão
8211002	Q-suco *light*
8211003	Q-refresko *light*
8211102	Q-suco *diet*

Soft Drinks

	Refrigerantes
8204902	Água tônica tradicional
8201202	Bidu tradicional
8200102	Coca-cola tradicional
8200202	Fanta laranja tradicional
8200505	Fanta uva tradicional
8200302	Guaraná tradicional
8200902	Minuano tradicional
8205402	Paraguai refrigerante tradicional
8200101	Refrigerante de cola tradicional
8200301	Refrigerante de guaraná tradicional
8203501	Refrigerante não especificado
8200407	Sprite refrigerante tradicional
8200208	Sukita tradicional
8201802	Tubaína tradicional
8201104	Mate tradicional

Soft Drinks (Diet/Light)

	Refrigerantes *diet/light*
8212902	Água tônica *diet*
8209002	Água tônica *light*
8200702	Coca-cola *light*
8201502	Fanta laranja *light*
8207705	Fanta uva *light*
8207402	Guaraná *diet*
8201602	Guaraná *light*
8209102	Paraguai refrigerante *light*
8200801	Refrigerante de cola *diet*
8200701	Refrigerante de cola *light*
8207401	Refrigerante de guaraná *diet*
8201601	Refrigerante de guaraná *light*
8207601	Refrigerante de limão *diet*
8212906	Refrigerante de quinino dietético
8201902	Tubaína *light*
8208104	Mate *light*

Other Nonalcoholic Beverages

	Outras bebidas não alcoólicas
8205803	Gatorade
8205901	Bebida energética
8202001	Caldo de cana
8202002	Garapa
8202101	Água de coco
8203603	Cevada
8203401	Levêdo de cerveja

Coffee

	Café
8501302	Café
8501303	Café com leite
8501304	Café tipo expresso
8501305	Café tipo *capuccino*
8202602	Nescafé
8206402	Café solúvel *capuccino*
8273902	Café com farinha
8212401	Café *capuccino* solúvel *light*
8212501	Café *capuccino* solúvel *diet*

Tea

	Chá
8213003	Chá mate orgânico
8213004	Chimarráo orgânico
8202803	Erva-mate
8202804	Chimarráo
8202805	Terere
8206301	Chá (preto, camomila, erva-cidreira, capim-limáo, etc.)
8205201	Chá *diet* (preto, camomila, erva-cidreira, capim-limáo, etc.)

Appendix IV: Evaluation of the Benzoate Acceptable Daily Intake

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Abbreviations

ADI	Acceptable Daily Intake
ADME	Adsorption, Distribution, Metabolism, and Excretion
AUC	Area Under the Curve
CCFA	Codex Committee on Food Additives
C_{max}	Maximum concentration of a drug achieved in a specified body compartment after the drug's administration and before the administration of a second dose
CSAF	Chemical-specific Adjustment Factor
CSF	Cancer Slope Factor
EFSA	European Food Safety Authority
EHC	Environmental Health Criteria
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor & Extract Manufacturers Association
FSANZ	Food Standards Australia New Zealand
GRAS	Generally Recognized as Safe
HBGV	Health-based Guidance Value
HED	Human Equivalent Dose
i.p.	Intraperitoneal
IPCS	International Programme on Chemical Safety
IUR	Inhalation Unit Risk
i.v.	Intravenous
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	Lethal Dose for 50% of Animals Tested
LOAEL	Lowest Observed Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NIH	National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
$PK_{inter}CSAF$	CSAF for Interspecies Pharmacokinetic Differences
$PK_{intra}CSAF$	CSAF for Intraspecies Pharmacokinetic Differences
POD	Point of Departure
RCT	Randomized Controlled Trial
RfC	Reference Concentration
RfD	Reference Dose
SCCP	Scientific Committee on Consumer Products
UF	Uncertainty Factor
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
WHO	World Health Organization

Executive Summary

Benzoic acid and its salts, particularly sodium and potassium benzoates, are commonly used as preservatives in acidic foods, beverages, pharmaceuticals, and cosmetic products. Sodium benzoate is also used as a therapeutic agent to treat urea cycle disorders and some neuropsychological conditions.

An acceptable daily intake (ADI) is a measure of the amount of a substance in food or drinking water that can be ingested on a daily basis over a lifetime without an appreciable health risk. Historically, a total uncertainty factor (UF) of 100 (10 for interspecies variability and 10 for intraspecies variability) has been used for deriving an ADI from animal toxicity data. Another contributor to the total UF is the database UF, which is used when there are substantial data gaps. In 2005, the International Programme on Chemical Safety (IPCS) published guidelines for developing chemical-specific adjustment factors (CSAFs) in place of default UFs. In these guidelines, IPCS suggested that based on empirical data: (1) the default UF of 10 for interspecies variability could be subdivided into a factor of 4 for pharmacokinetics and 2.5 for toxicodynamics, (2) the default UF of 10 for human variability could be subdivided into two equal subfactors of 3.16, and (3) quantitative data could be used to derive CSAFs to replace these default values. The Joint World Health Organization (WHO)/Food and Agriculture Organization (FAO) Expert Committee on Food Additives (JECFA) has sub-divided UFs of 10 in several prior evaluations.

In 2000, JECFA maintained its group ADI of 0-5 milligrams per kilograms of body weight per day (mg/kg bw-day) for benzoic acid, its salts, and its precursor compounds based on a four-generation rat study conducted in 1960 with a no observed adverse effect level (NOAEL) of 500 mg/kg bw-day, the highest dose tested in the study. It then applied a total UF of 100 – 10 for database uncertainty and 10 for interspecies variability. However, JECFA did not evaluate human variability, nor did it give a rationale for not considering the intraspecies variability UF.

Many studies on benzoic acid and its salts have been conducted since the ADI was first derived, including toxicity, pharmacokinetic, and clinical studies. It is striking that data from all these studies are consistent. Collectively, they support lowering the UFs for deriving the ADI for benzoic acid and its salts.

The pharmacokinetics of sodium benzoate and benzoic acid are similar in rats and humans. Quantitative comparisons of areas under the curve (AUCs) support a CSAF of 1.2 for interspecies variability in pharmacokinetics. In addition, data from healthy adults and children with urea cycle defects support a CSAF of 1.4 for human variability in pharmacokinetics.

The animal toxicity database for oral exposures to benzoic acid, its salts, and its precursor compounds includes acute and chronic toxicity, reproductive/developmental toxicity, carcinogenicity, and genotoxicity studies. These studies consistently report a lack of toxicity in several animal species at doses up to 1,000 mg/kg bw-day. Human clinical data on sodium benzoate as a therapeutic agent provide additional evidence supporting the lack of toxicity at comparable doses. This indicates that using the UF for database uncertainty is not warranted in this case.

Clinical studies of sodium benzoate efficacy, which have not yet been considered by JECFA, demonstrate that treatment with doses up to 500 mg/kg bw-day are well tolerated in humans, including neonates and infants, with no apparent adverse effects. The highest human NOAEL of sodium benzoate, as suggested by these clinical data, (500 mg/kg bw-day, equivalent to 423.7 mg/kg bw-day benzoic acid) is comparable

to the rodent NOAEL of 500 mg/kg bw-day of benzoic acid, thus providing supporting evidence that the UFs for interspecies differences and intraspecies differences in toxicodynamics could also be reduced or possibly eliminated.

An evaluation of the currently available data on benzoate supports a total UF of 13: 1.2 for interspecies variability in pharmacokinetics, 1.4 for human variability in pharmacokinetics, 2.5 for interspecies differences in toxicodynamics, and 3.16 for human variability in toxicodynamics. The UF of 13, which is based on robust data from the published literature, instead of the default value of 100, results in an ADI of 0-38 mg/kg bw-day.

1 Background

Benzoic acid is naturally produced by many plants, with high concentrations found in certain berries. It inhibits the growth of mold, yeast, and some bacteria (Brul and Coote, 1999; Nair, 2001). Because of this, benzoic acid and its salts, particularly sodium and potassium benzoates, are commonly used as preservatives in acidic foods, beverages, pharmaceuticals, and cosmetic products (Nair, 2001; JECFA, 2015, 2016). Sodium and, to a lesser extent, potassium benzoates are preferred for use in beverages, rather than benzoic acid, because of their increased water solubility.

Benzoic acid, sodium benzoate, and potassium benzoate are considered safe by many regulatory agencies around the world. For example, they are "generally recognized as safe" (GRAS) for current use in food by the United States Food and Drug Administration (US FDA, 1973a,b, 2016), and Food Standards Australia New Zealand (FSANZ) concluded that it is unlikely that the current levels of benzoates in foods pose a risk to consumers, including children (FSANZ, 2016).

In addition to its use as a preservative, sodium benzoate is used in pharmaceuticals to treat urea cycle disorders because it can bind amino acids (IOMC, 2000). Currently, there are three US FDA-approved drugs that contain sodium benzoate as one of the main active ingredients (Ammonul®, a generic version of Ammonul®, and Ucephan®), as indicated in the Drugs@FDA online database for US FDA-approved drug products. Therapeutic doses of sodium benzoate can be as high as 250-500 milligrams per kilograms of body weight per day (mg/kg bw-day), equivalent to 211.9-423.7 mg/kg bw-day benzoic acid, and are up to two orders of magnitude higher than exposure levels from dietary intake (IOMC, 2000). Notably, no serious side effects have been reported after therapeutic uses of sodium benzoate (IOMC, 2000).

According to the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA), the toxicity of benzoic acid and its salts in rodents is low. Based on a four-generation study in rodents conducted in 1960 (Kieckebusch and Lang, 1960), JECFA identified a no observed adverse effect level (NOAEL) of 500 mg/kg bw-day based on the highest dose tested in the study. An uncertainty factor (UF) of 100 was applied to the NOAEL to yield an acceptable daily intake (ADI) for benzoic acid, its salts, and its precursor compounds of 0-5 mg/kg bw.[1] This ADI first appeared in the sixth JECFA report in 1962. The basis of the UF was not specified in this report (JECFA, 1962). The ADI was finalized in a 1996 JECFA assessment, in which the rationale for applying a UF of 100 was again not given (JECFA, 1997). In 2000, JECFA maintained the group ADI of 0-5 mg/kg bw-day and specified that the total UF of 100 included 10 for database uncertainty and 10 for interspecies variability (IOMC, 2000). However, JECFA did not consider a UF for human variability. It is unclear why this is the case, because, historically, a default UF of 100, based on a factor of 10 for interspecies variability and another factor of 10 for intraspecies variability, has been used when JECFA derives an ADI from a NOAEL based on animal toxicity data.

Recently, JECFA conducted a comprehensive dietary assessment on benzoates and determined that high-end dietary exposures to benzoates in children, including toddlers and young children (1-7 years of age) and other children (8-17 years of age), exceed the upper bound of the current ADI (5 mg/kg bw-day) (JECFA, 2015, 2016). Based on this, the Codex Committee on Food Additives (CCFA) lowered the interim maximum level of benzoates in beverages by more than 50% generally and by 75% in some

[1] Traditionally, JECFA has developed ADIs as ranges, from 0 to an upper limit.

instances. However, the safety database on benzoic acid, its salts, and its precursor compounds has expanded considerably since the ADI was developed in the early 1960s. Thus, we evaluated available animal toxicity data, animal and human pharmacokinetic data, and human clinical data to determine whether the UF of 100 is still justified, or whether the evidence supports reducing the total UF used to derive the ADI. We found that the available evidence supports a revision of the total UF, which results in a revised ADI of 0-38 mg/kg bw-day based on the available robust data in humans and rats.

2 Risk Assessment Guidelines

Chemical risk assessment, defined as "the characterization of the potential adverse health effects of human exposures to environmental hazards" (NRC, 1983), provides the scientific basis for many risk management decisions pertaining to chemicals in food and the environment. Chemical risk assessment involves the following four steps.

1. **Hazard Identification:** To determine whether a particular chemical is causally linked to adverse health effects.
2. **Hazard Characterization/Dose-Response Assessment:** To evaluate the relationship between the magnitude of exposure to the chemical and the probability of the occurrence of the adverse health effect.
3. **Exposure Assessment:** To estimate the level of human exposure to the chemical hazard.
4. **Risk Characterization:** To determine whether individuals exposed to the chemical in question will experience adverse health effects by comparing the estimated exposure level to the value obtained from the dose-response assessment, with an assessment of the magnitude of uncertainty.

Quantification of human health risks combines information regarding exposure with dose-response information, as reflected in chemical-specific toxicity criteria. For chronic non-cancer effects, toxicity is typically characterized using a health-based guidance value (HBGV). HBGVs are defined by the WHO as "levels of human exposure considered to be 'without appreciable health risk'" (IPCS, 2009, p. liii). A specific reference dose (RfD) is established for chemicals that may be ingested or absorbed through the skin, and a reference concentration (RfC) is established for chemicals that may be inhaled. For food additives, the HBGV is commonly known as the ADI, as defined by the Environmental Health Criteria (EHC) 240 Principles and Methods for the Risk Assessment of Chemicals in Food (IPCS, 2009). For cancer, toxicity is typically characterized using a linear cancer slope factor (CSF) for a non-threshold response resulting from oral and dermal exposures or an inhalation unit risk (IUR) factor for chemicals that are inhaled. However, there is an ongoing debate about whether a threshold approach may be pursued (*e.g.*, Bolt, 2003; Lutz and Lutz, 2009; Bogen, 2016; Greim and Albertini, 2012a,b).

A number of authoritative scientific and regulatory bodies have published guidelines for risk assessment (NRC, 1983; US EPA, 2002, 2004; IPCS, 2009). In 2009, the International Programme on Chemical Safety (IPCS), a collaboration between three United Nations bodies – the WHO, the International Labour Organization, and the United Nations Environment Programme – published EHC 240 guidelines on the risk assessment of chemicals in food, such as food additives, pesticides, veterinary drug residues, and contaminants (IPCS, 2009).

In line with other guidelines, the 2009 EHC 240 guidelines specify:

> Evaluations of food additives by JECFA depend on studies performed with a chemical substance or product of defined identity, purity and physical form. The safety assessment is valid only for products that do not differ significantly in identity and quality profile from the material used to generate the data used in the evaluation. (IPCS, 2009, p. xlv)

For hazard identification, the 2009 EHC 240 guidelines state:

> Study of the absorption, distribution, metabolism and excretion (ADME) of a substance at an early stage of testing is important in aiding the selection of appropriate test species and test doses for toxicity studies. Where possible, investigation of any qualitative or quantitative differences in ADME between the test species and humans will provide important information for characterization of the hazard. (IPCS, 2009, p. xlvii)

Regarding toxicity testing, the 2009 EHC 240 IPCS guidelines state:

> The extent of toxicological testing required depends on the nature and use of the substance under consideration… Short-term and long-term tests for general systemic toxicity are usually conducted. These identify target organs for toxicity and may indicate the need for additional or more specific testing (e.g. for neurotoxicity or immunotoxicity). The effects of the test substance on a wide range of end-points indicative of toxicity, including observational, functional, biochemical and pathological end-points, are examined. Studies are typically conducted in two species, either a rodent and a non-rodent species or two rodent species, and in both sexes, to maximize the opportunity to find any effects. (IPCS, 2009, p. xlvii)

The 2009 EHC 240 guidelines also specify:

> Testing should be conducted in a manner that best relates to human exposure scenarios. Dose selection should take into account the anticipated human exposure, the frequency of exposure and the duration of exposure. For substances present in foods, administration of the substance in repeated-dose animal studies is usually by diet, gavage or drinking-water. Ideally, the dose levels selected are such that toxic effects, but not death or severe suffering, are produced at the highest dose level, with lower dose levels producing graded responses and no adverse effects at the lowest dose level. The study design should be adequate to determine a reference point for hazard characterization, also known as a point of departure (POD), such as a no-observed-adverse-effect level (NOAEL) or a benchmark dose (BMD), which is a dose producing a low but measurable adverse response. (IPCS, 2009, p. xlviii)

With regard to human studies, the 2009 EHC 240 guidelines state:

> Data from human studies are of potential importance in identifying and characterizing hazards and evaluating the risks of food additives, contaminants and residues of veterinary drugs and pesticides. The information may come from controlled experiments in human volunteers, surveillance studies, epidemiological studies (e.g. ecological studies, case–control studies, cohort studies, analytical or intervention studies) of populations with different levels of exposure, experimental or epidemiological studies in specific subgroups of people, or clinical reports (e.g. poisoning) or case-studies of individuals. End-points may include examination of safety or tolerance, nutritional and functional effects of foods or food components, the metabolism and toxicokinetics of the substance, mode of action, possibly using biomarkers for effects identified in animal studies, and adverse health effects from unintentional exposures (e.g. to a contaminant). (IPCS, 2009, p. li)

To derive HBGVs, the 2009 EHC 240 guidelines state:

> Health-based guidance values are derived from the dose-response assessment for the most relevant end-point in the most relevant species. The first approach, which is the one still most commonly used by JECFA and JMPR to derive health-based guidance values in order to protect against effects considered to have a threshold, is to define the NOAEL or sometimes a lowest-observed-adverse-effect level (LOAEL) as the POD. The other approaches that have been used by JECFA and JMPR are to use the lower one-sided confidence limit of the BMD (the BMDL) as the POD for the derivation of a health-based guidance value or for calculation of a margin of exposure (MOE). (IPCS, 2009, p. liv)

To calculate an HBGV (*e.g.*, the ADI for food additives), an overall adjustment or UF is usually applied to the NOAEL or lowest observed adverse effect level (LOAEL) identified from toxicity studies to account for, among other things, human variability as well as the inherent uncertainties when extrapolating toxicity data from experimental animals to potential health effects in humans. Conventionally, a total UF of at least 100 – 10 for interspecies variability and 10 for intraspecies variability – has been used when an ADI is derived from animal toxicity data. Other UFs that are sometimes applied when deriving an HBGV include the LOAEL UF, if a LOAEL is used as the point of departure (POD) instead of a NOAEL, and the database UF, if there are substantial data gaps.

In 2005, IPCS published guidelines on chemical-specific adjustment factors (CSAFs), which allow the use of specific data on species differences or human variability in either pharmacokinetics or toxicodynamics to derive data-driven UFs in place of default factors, when possible (IPCS, 2005). Based on empirical information, the IPCS CSAF guidelines indicate that the default UFs for interspecies differences and human variability should be divided into pharmacokinetic and toxicodynamic components. Briefly, pharmacokinetics describe the adsorption, distribution, metabolism, and excretion (ADME) of a substance, whereas toxicodynamics generally describe the effect of a substance and its mode of action. For the interspecies UF, IPCS indicates that the default value of 10 can be subdivided into a factor of 4 for pharmacokinetics and 2.5 for toxicodynamics, and for human variability, the default UF value of 10 can be subdivided into two equal subfactors of 3.16. The IPCS CSAF guidelines also describe data requirements and considerations for the development of CSAFs for interspecies differences and human variability in pharmacokinetics and toxicodynamics. JECFA has set a precedent for using CSAFs. For example, it subdivided UFs of 10 in its evaluations of dioxins (JECFA, 2002) and methylmercury (JECFA, 2004).

In the following sections, we review the current safety database on benzoic acid, its salts, and its precursor compounds, which includes animal toxicity data, animal and human pharmacokinetic data, and human clinical data, to determine whether the evidence supports reducing the UFs used to derive the ADI for these related substances.

3 Animal Toxicity Data

Benzoic acid and its salts have a long history of safe use as food additives. A number of scientific and regulatory bodies, including JECFA, the Organisation for Economic Co-operation and Development (OECD), the European Food Safety Authority (EFSA), the Flavor & Extract Manufacturers Association (FEMA), and the European Commission Scientific Committee on Consumer Products (SCCP), have conducted comprehensive assessments and safety profiles for benzoic acid, its salts, and some of its precursor compounds, such as benzyl alcohol, benzyl acetate, and benzaldehyde (Adams *et al*., 2005; EFSA, 2016; IOMC, 2000; JECFA, 1997; OECD, 2001; Nair, 2001; SCCP, 2005). We relied on these assessments, particularly more recent ones (Adams *et al*., 2005; SCCP, 2005; EFSA, 2016), when evaluating the current toxicity database. Because our safety evaluation of benzoic acid and its salts is conducted in the context of food additives, we focused on oral exposure, with an emphasis on chronic exposure. Below, we briefly summarize this evidence. Detailed evaluations and specific references can be found in the aforementioned assessments (SCCP, 2005; Adams *et al*., 2005; EFSA, 2016).

The acute oral toxicity potential of benzoic acid and its salts is low. The LD_{50}[2] for benzoic acid and its salts ranges from 1,200-4,070 mg/kg bw in rats and mice in previous studies (SCCP, 2005; EFSA, 2016).

The available short-term and subchronic studies in rats and mice indicate that benzoic acid and its salts have low toxicity and no marked target organ toxicity. No treatment-related adverse effects were observed after oral exposure to benzoic acid or sodium benzoate for 10-90 days at concentrations of 1,000 mg/kg bw-day or below (SCCP, 2005; EFSA, 2016).

Regarding genotoxicity, some equivocal results have been observed in lower-quality *in vitro* studies (*e.g.*, with poor reporting, inappropriate controls, a lack of negative controls, and/or doses exceeding the limit dose). However, these results were outweighed by the lack of genotoxicity established in several robust, well performed, relevant *in vivo* studies. JECFA and other regulatory and scientific entities have concluded that, taken together, the weight of the evidence indicates that benzoic acid and its salts are not genotoxic (SCCP, 2005; EFSA, 2016).

Carcinogenicity studies in rats (up to 1,000 mg/kg bw-day for 2 years) and mice (approximately 5,900-6,200 mg/kg bw-day for their lifetimes) demonstrate that benzoic acid, its salts, and its precursor compounds do not cause tumors in tested animals (SCCP, 2005; EFSA, 2016).

The developmental toxicity of benzoic acid and its salts has been evaluated in a number of studies in rats, mice, hamsters, and rabbits (SCCP, 2005; EFSA, 2016). With few exceptions, these studies did not report any developmental toxicity at the highest doses tested, and study-specific NOAELs range from 160-500 mg/kg bw-day. One study that reported developmental toxicity also reported severe maternal toxicity after exposure to 1,875 mg/kg bw-day of sodium benzoate (equivalent to 1,589 mg/kg bw-day of benzoic acid) *via* the diet, indicating that the developmental toxicity was likely a secondary effect. This study reported a NOAEL of 1,310 mg/kg bw-day for sodium benzoate, equivalent to 1,110 mg/kg bw-day for benzoic acid (Onodera *et al*., 1978, as cited in EFSA, 2016). Another study in rats exposed to benzoic acid by gavage reported maternal and developmental toxicity at 450 mg/kg bw-day and a NOAEL of 160 mg/kg bw-day (EPA, 1992, as cited in EFSA, 2016).

[2] The LD_{50} is the statistically derived single dose of a substance that can be expected to cause death in 50% of the animals tested (Klaassen and Watkins, 2003).

Only one multi-generation reproductive toxicity study of benzoic acid has been conducted (Kieckebusch and Lang, 1960). In this study, three groups of 20 male and 20 female white rats were pair-fed for 8 weeks on a standard diet with either 0%, 0.5%, or 1% benzoic acid (equivalent to 0, 250, or 500 mg/kg bw-day). The rats were fed *ad libitum* over four generations, with the first two generations fed for their whole lifespan and the third and fourth generations autopsied after 16 weeks on the diet. No treatment-related effects were observed for growth, fertility, lactation, or organ weights; there were also no histopathological findings in organs at the highest dose tested. In addition, reproductive toxicity studies of benzoic acid's precursor compounds (*i.e.*, benzyl alcohol, benzyl acetate, and benzaldehyde) generally indicated no toxicity at doses at or below 500 mg/kg bw-day (IOMC, 2000; SCCP, 2005).

The NOAEL of 500 mg/kg bw-day identified in Kieckebusch and Lang (1960) was selected by JECFA as the POD for derivation of the ADI for benzoic acid and sodium benzoate (JECFA, 1997). JECFA applied a UF of 10 for database uncertainty. Although most toxicity studies were conducted decades ago, as discussed above, they consistently report a lack of toxicity for a variety of endpoints in several animal species at doses up to 1,000 mg/kg bw-day. Human clinical data on sodium benzoate as a therapeutic agent provide additional evidence supporting the lack of toxicity at doses comparable to the NOAELs identified in laboratory animal studies (discussed in Section 5). Considering the collective evidence in both experimental animals and humans, the UF for database uncertainty is not warranted.

4 Pharmacokinetic Data in Humans and Experimental Animals

After ingestion, benzoic acid is quickly absorbed and primarily metabolized in the liver by conjugation with glycine, resulting in the formation of hippuric acid (Tremblay and Qureshi, 1993; Informatics, Inc., 1972). In humans and rats, the conversion of benzoate to hippurate also takes place in the kidneys, although to a lesser extent than it does in the liver (Tremblay and Qureshi, 1993). Benzoic acid is rapidly converted to the intermediate, benzoyl-CoA, which is subsequently conjugated with glycine in a reaction catalyzed by the enzyme glycine N-acyltransferase (Tremblay and Qureshi, 1993; Informatics, Inc., 1972). Studies have shown that the formation of hippuric acid is limited by glycine availability, because this pathway is saturated at high benzoate/benzoic acid doses (Tremblay and Qureshi, 1993; Informatics, Inc., 1972; Adams *et al*., 2005). Benzoyl glucuronide, a minor metabolite of benzoic acid, is only seen in humans after very high doses (>500 mg/kg bw) of sodium benzoate exposure (Informatics, Inc., 1972; IOMC, 2000).

The EHC 240 risk assessment guidelines specify that the evaluation of qualitative and quantitative differences in ADME between experimental animals and humans greatly informs hazard identification and risk characterization (IPCS, 2009). EFSA (2016) concluded in its most recent assessment that the available data on the ADME of benzoic acid and its sodium and potassium salts indicate sufficiently similar patterns (after ingestion, benzoate salts are rapidly converted to benzoic acid *in vivo* due to the acidic environment in the stomach), and thus read-across between substances is appropriate.

We evaluated the robust pharmacokinetic data available in humans and animals for benzoic acid, its salts, and its precursor compounds to determine whether the pharmacokinetics of these compounds are comparable in humans and animals, particularly rats,[3] and further explored whether the pharmacokinetics are similar among humans. Based on this, we derived CSAFs to account for interspecies and intraspecies differences in pharmacokinetics of benzoic acid and sodium benzoate.

4.1 Pharmacokinetics of Benzoic Acid and Its Salts in Humans

Sodium benzoate is used in pharmaceutical drugs, often with sodium phenylacetate, to treat urea cycle disorders because it acts as an amino acid scavenger (IOMC, 2000). In addition to pharmacokinetic studies of benzoic acid and sodium benzoate, clinical studies of therapeutic drugs containing sodium benzoate, involving infants, children, and adults, have also provided robust pharmacokinetic information. The pharmacokinetic data from these studies are described below.

Bridges *et al*. (1970) evaluated the urinary excretion of radiocarbon [^{14}C]-labeled benzoic acid administered orally (1 mg/kg bw) to two adult humans. They excreted all the [^{14}C] within 24 hours and entirely as hippuric acid. Similar results were observed by Simell *et al*. (1986), who evaluated the effects of intravenous (i.v.) administration of 2 mmol/kg bw (approximately 288 mg/kg bw) sodium benzoate plus L-alanine (6.6 mmol/kg) to five Finnish children aged 2.8-12.6 years (mean of 8.8) with a urea cycle disorder (lynsinuric protein intolerance). The authors reported that peak plasma benzoic acid concentrations of 5.1-6.2 mM were observed at approximately 2 hours following the infusion and that the

[3] The current ADI is based on a NOAEL obtained from a study in rats (Kieckebusch and Lang, 1960).

majority of administered benzoate was excreted as hippuric acid, with less than 2% excreted as unchanged benzoate in the urine in 24 hours.

Two independent pharmacokinetic studies in healthy human volunteers were conducted with the drug Ammonul (10% sodium benzoate/10% sodium phenylacetate) (US FDA, 2004a; MacArthur *et al*. 2004).[4] In one study, 20 healthy adult volunteers were administered Ammonul *via* i.v. infusion at doses of 5.5 g/m^2 or 3.75 g/m^2 (approximately 150 or 100 mg/kg bw sodium benzoate, respectively[5]) for an initial 90-minute loading infusion followed by a 24-hour sustained infusion (US FDA, 2004a; MacArthur *et al*., 2004).[6] Sodium benzoate demonstrated saturable elimination with decreased clearance with increased dose. The authors also noted a greater than dose-proportional increase in both area under the curve (AUC) and C_{max}[7] for benzoic acid. The AUC for the sodium benzoate metabolite (hippurate) increased proportionally with dose, though the increase in C_{max} was less than dose proportional. The authors noted no marked sex differences. In the second study, similar results were obtained for parent compounds and metabolites with escalating dose (1, 2, and 4 g/m^2) (US FDA, 2004a). The AUC and C_{max} for benzoic acid increased in a greater than dose-proportional manner and hippurate AUC increased proportionally with dose.

Kubota *et al*. (1988) evaluated benzoic acid and hippuric acid in the plasma and urine of one healthy 33-year-old male who consumed three oral doses of sodium benzoate in water (40, 80, and 160 mg/kg). The authors did not detect benzoic acid in the urine after administration of any dose. In the subject's plasma, Kubota *et al*. (1988) found that peak concentrations of benzoic acid occurred at 0.5, 1.5, and 2 hours, and observed peak plasma concentrations of hippuric acid levels at 1, 2, and 4.5 hours after exposure to 0.04, 0.08, and 0.16 g/kg sodium benzoate, respectively. The investigators also found a disproportionate increase in the plasma benzoic acid AUC, a proportional increase in the hippuric acid AUC with increasing dose, and peak plasma and urinary excretion rates of hippuric acid independent of dose levels. The investigators noted that these results indicate that the biotransformation of benzoic acid to hippuric acid in the human body is saturable and non-linear.

Similar trends were observed in a later study by Kubota and Ishizaki (1991), who administered oral doses of sodium benzoate (40, 80, or 160 mg/kg bw) at least 1 week apart to six healthy adult men (22-34 years of age). As observed by Kubota *et al*. (1988), the AUC of plasma benzoic acid did not increase proportionally with dose; the AUCs after 80 and 160 mg/kg bw sodium benzoate were 3.7- and 12.0-fold greater, respectively, than the AUC after the lowest dose of 40 mg/kg. The mean AUC of hippuric acid was approximately proportional to the sodium benzoate dose. The study also found that the rate of biotransformation of benzoic acid to hippuric acid varied among subjects (17.2-28.8 mg/kg bw-hour), with a mean value of 23.0 mg/kg bw-hour. The investigators suggested this rate is close to that obtained after the daily maximum dose of 500 mg/kg bw-day sodium benzoate, which they noted is the recommended dose for treatment of hyperammonemia in patients with inborn errors of ureagenesis.

Oyanagi *et al*. (1987) evaluated the pharmacokinetics of sodium benzoate in two patients: one 10-year-old girl with partial ornithine transcarbamylase deficiency ("patient 1") and one 22-year-old man with partial argininosuccinate synthetase and arginase deficiencies ("patient 2"). The investigators observed peak serum benzoic acid concentrations at 1 and 2 hours after the dose in patients 1 and 2, respectively.

[4] Upon administration, phenylacetate conjugates with glutamine in the liver and kidneys to form phenylacetylglutamine, *via* acetylation, and is then excreted by the kidneys. The metabolic process of phenylacetate is distinct from that of benzoate, so the pharmacokinetic data of these two substances can be evaluated independently.

[5] Based on a conversion factor (k_m) of 37 to convert doses units of mg/m^2 to mg/kg bw for adult humans (US FDA, 2005).

[6] A dose of 5.5 g/m^2 caused severe emesis in first three patients; the dose was then reduced to 3.75 g/m^2 for the remaining 17 subjects.

[7] C_{max} is the maximum concentration of a drug achieved in a specified body compartment after the drug's administration and before the administration of a second dose.

Similar to the results observed in the studies discussed previously (*i.e.*, US FDA, 2004a; MacArthur *et al*., 2004; Kubota *et al*., 1988; Kubota and Ishizaki, 1991), the decrease in serum benzoate did not follow linear elimination kinetics.

In a study of four neonates administered 3.5 mmol/kg bw-day (460 mg/kg bw-day) sodium benzoate *via* i.v. injection, Green *et al.* (1983) found large inter-patient variability in benzoate metabolism, observing an eight-fold range in serum benzoate concentrations (2.14-16.0 mmol/L) after sodium benzoate administration for ≥24 hours. Mean serum benzoate and hippurate concentrations after ≥24 hours of benzoate treatment were 7.38 ± 6.39 mmol/L and 1.14 ± 0.64 mmol/L, respectively, and 84% of the administered benzoate was excreted as benzoate and hippurate in the urine (reviewed in Batshaw *et al*., 2001). Serum ammonia and glycine concentrations remained within the normal range for all participants throughout the study. The observed variability in benzoate metabolism may have been related to reduced renal clearance or limited benzoate conjugation capacity in these neonates (Batshaw *et al*., 2001).

In a clinical study of children with inborn errors of urea synthesis, Brusilow *et al*. (1984) documented the time course of plasma benzoate concentrations in two infants (aged 12 and 5 months) after receiving a single dose of sodium benzoate (250 mg/kg bw) and sodium phenylacetate (250 mg/kg bw) *via* i.v. administration. The plasma benzoate concentrations in these two infants rose quickly and peaked at 3.2 mM and 2.5 mM at 1 and 2.7 hours, respectively, following i.v. infusion. Sodium benzoate appeared to be completely metabolized within 10 and 20 hours of i.v. infusion, respectively. In addition, the high plasma concentrations of glycine in these two infants at admission declined following benzoate treatment.

Lennerz *et al*. (2015) recently evaluated the effects of sodium benzoate on glucose homeostasis and human metabolic profiles by administering "GRAS levels" (0.1% [490 mg] in a beverage) of sodium benzoate to 14 overweight adults. The mean sodium benzoate dose administered was equivalent to 4.79 mg/kg bw (range: 3.8-5.9 mg/kg bw per dose) benzoic acid. The investigators observed a rapid rise in plasma benzoate and hippurate levels with the peak concentration (C_{max} of approximately 2.5 and 87.5 µg/mL, respectively)[8] at 0.5 hours after consumption, and a decline to baseline levels by 2 hours for both metabolites. Lennerz *et al*. (2015) also found that following consumption of a second glucose-containing beverage with sodium benzoate, the rise in benzoate and hippurate was significantly attenuated. The authors speculated that glucose may have down-regulated the uptake of benzoate in the digestive tract and the clearance of plasma benzoate and hippurate. The authors also noted that the time window of plasma measurements was narrow and may have missed the peak concentrations of these metabolites. Given the limitations of this study, it is difficult to draw any firm conclusion with regard to whether or not glucose may interfere with the uptake and clearance of benzoate. However, it is evident that sodium benzoate had no significant effect on glucose homeostasis as measured by comparisons of glucose and insulin levels with or without sodium benzoate exposure.

4.2 Pharmacokinetics of Benzoic Acid and Its Salts in Experimental Animals

Animal studies that provide robust pharmacokinetic information on benzoic acid, its salts, and its precursor compounds are described below.

Bridges *et al*. (1970) studied the urinary excretion of radiocarbon [^{14}C]-labeled benzoic acid administered orally to various animal species. At a dose of 50 mg/kg bw, benzoic acid was excreted by rodents (rats, mice, guinea pigs, golden hamsters, steppe lemmings, and gerbils), rabbits, cats, and capuchin monkeys almost entirely as hippuric acid (95-100% of 24-hour excretion). This is similar to humans and rhesus monkeys, in which 1 or 20 mg/kg bw benzoic acid, respectively, was excreted entirely as hippuric acid.

[8] C_{max} was obtained through analysis of published figures and the use of GetData software.

Other species, such as the squirrel monkey, pig, dog, ferret, hedgehog, and pigeon, excreted a dose of 50 mg/kg bw benzoic acid as 80% hippuric acid and 20% benzoyl glucuronide and benzoic acid. Humans and rats excreted about 99 and 100% of the original benzoic acid dose in 24 hours, respectively, whereas many other species excreted less over the same period (*e.g.*, rhesus monkeys excreted 47% in 24 hours).

Thabrew *et al*. (1980) confirmed the observations of Bridges *et al*. (1970), demonstrating that 99% of [^{14}C]-labeled benzoic acid administered to Wistar albino rats *via* intraperitoneal (i.p.) injection was excreted as hippuric acid, with 75-90% of the [^{14}C] excreted within 24 hours. These results were also consistent with those of Kao *et al*. (1978), who evaluated benzoic acid metabolism in isolated kidney tubules and liver hepatocytes from rats *in vitro*. The authors found that both liver and kidney cells are capable of metabolizing benzoic acid *in vitro*, hippuric acid is the primary metabolite in both cell types, and liver cells have a higher rate of hippuric synthesis and glycine conjugation of benzoic acid than the kidney cells.

Simkin and White (1957) evaluated the effect of benzoate administration (*via* i.p. injection) on free glycine levels in the blood, liver, and muscle, and urinary hippuric acid concentration in female rats and rabbits fed a glycine-poor diet. Liver glycine fell to about 50% of the initial level within 0.5-1 hour after dosage in rats; the relative magnitude of the change appeared to be independent of the size of the dose (170-470 µmoles/100 g bw, or approximately 240-680 mg/kg bw[9]). A smaller decrease in blood free glycine levels (about 80% of the initial level) was also observed in rats; this effect was also unrelated to dose level. The investigators observed hippuric acid excretion to be complete 4 hours after benzoate administration in rats. Similar results for free blood glycine and hippuric acid excretion were obtained in experiments with rabbits.

In a liver perfusion study, Schwab *et al*. (2001) evaluated hepatic uptake and metabolism of benzoate in rats. The authors confirmed that benzoate is metabolized exclusively to hippurate and observed a plateau of hippurate formation with increasing unbound plasma benzoate concentrations, indicating saturation of benzoate conjugation. Similarly, Gregus *et al*. (1992) investigated glycine conjugation capacity by administering sodium benzoate *via* i.v. injection (0.2-2 mmol/kg bw to rats) to evaluate changes in blood levels of benzoate as well as blood and urinary levels of benzoylglycine, the glycine-conjugated metabolite of benzoate/benzoic acid. In addition to confirming that benzoylglycine is the "only significant" mechanism of benzoic acid elimination, the investigators observed a dose-dependent decrease in the benzoate elimination rate and blood clearance with an unchanged volume of distribution (Gregus *et al*., 1992). The blood concentration and urinary excretion rate of benzoylglycine also reached maximal values with increasing sodium benzoate doses. Together, these findings indicate that benzoylglycine formation is capacity-limited at higher doses. Thus, like other studies, the results from both the Schwab *et al*. (2001) and Gregus *et al*. (1992) studies indicate that benzoic acid metabolism/excretion is: (1) limited by glycine capacity, and (2) a saturable process at higher exposures.

[9] Based on the molecular weight of sodium benzoate (144.11 g/mol) and the body weight of the albino rats, given in the study as 130-170 g (Simkin and White, 1957).

4.3 Comparison of Human and Rat Pharmacokinetics of Benzoic Acid and Its Salts

4.3.1 Qualitative Comparison

The ADME of benzoic acid and its sodium and potassium salts are sufficiently similar to allow read-across between these compounds (EFSA, 2016). We used this approach in our analysis to compare the pharmacokinetics of these substances in humans and laboratory animals.

After oral ingestion, benzoic acid and its salts are primarily metabolized in the liver by conjugation with glycine, resulting in the formation of hippuric acid (Tremblay and Qureshi, 1993; Informatics, Inc., 1972). In humans and most of the animal species studied (including rats), benzoyl glucuronide appears to be a minor secondary metabolite.

Benzoic acid sometimes appears in its free form in urine (Informatics, Inc., 1972; Bridges *et al*., 1970; Kao *et al*., 1978). The amount of benzoate excreted as hippuric acid is similar in rats and humans: 75-100% of benzoic acid is excreted as hippuric acid within 6-24 hours in both species (IOMC, 2000; Bridges *et al*., 1970; Thabrew *et al*., 1980).

Largely due to the rapid metabolism and excretion, benzoate and benzoic acid do not accumulate in humans (Bridges *et al*., 1970; Kubota *et al*., 1988; Kubota and Ishizaki, 1991) or rats (reviewed by Informatics, Inc., 1972; FASEB, 1973; IOMC, 2000; OECD, 2001; JECFA, 1996; SCCP, 2005; EFSA, 2016).

At high exposures to benzoic acid and its salts (*i.e.*, >400 mg/kg in rats and ≥160 mg/kg in humans), hippuric acid formation can be limited by the availability of glycine, and the benzoyl glucuronide metabolite appears after the depletion of glycine (Simkin and White, 1957; MacDermot *et al.*, 1981; Kubota and Ishizaki, 1991; reviewed in Tremblay and Qureshi, 1993 and Adams *et al*., 2005). However, humans can produce enough glycine to conjugate approximately 1,300 mg of sodium benzoate per hour (equivalent to 21.7 mg sodium benzoate/kg bw, assuming a standard adult body weight of 60 kg) or 1,500 mg benzoic acid per hour (equivalent to 25 mg benzoic acid/kg bw, assuming a standard adult body weight of 60 kg) (Informatics, Inc., 1972; Bridges *et al*., 1970; Kubota *et al*., 1988).

In humans, peak plasma benzoic acid levels are reached 1-2 hours after oral ingestion of sodium benzoate (Kubota *et al*., 1988; Kubota and Ishizaki, 1991). Similar quantitative information in rats is limited to the administration of the benzoic acid precursor, benzyl acetate (500 mg/kg bw), *via* gavage (Yuan *et al*., 1995, as cited in Adams *et al*., 2005). In the Yuan *et al*. (1995, as cited in Adams *et al*., 2005) study, peak benzoic acid plasma levels were reached within 3 hours of administration.

The extensive pharmacokinetic data available in humans indicate that the biotransformation of benzoic acid and its salts is a saturable process following Michaelis-Menten kinetics (Kubota *et al*., 1988; Kubota and Ishizaki, 1991; MacArthur *et al*., 2004; reviewed in IOMC, 2000 and JECFA, 1996). This is supported by studies showing that benzoic acid clearance increased disproportionately to the administered dose (ranging from 40-160 mg/kg bw), while hippuric acid clearance was proportional to dose. In these studies, peak plasma benzoic acid concentrations increased with increasing dose while peak hippuric acid concentrations did not change. While the animal database is less robust than the human database, the available evidence indicates that there is a similar saturable process for benzoate metabolism at high exposures (*i.e.*, >120 mg/kg bw) (Schwab *et al*., 2001; Gregus *et al*., 1992; Simkin and White, 1957;

Bray *et al*., 1951). Overall, the general pharmacokinetic mechanisms of benzoic acid and its salts are very similar in humans and rats (Table 4.1).

Table 4.1 Pharmacokinetics of Benzoic Acid and Its Salts in Humans and Rats

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

Notes:
(a) Data from study of F344 rats administered 500 mg/kg benzyl acetate *via* gavage (Yuan *et al*., 1995, as cited in JECFA, 1996).
(b) Data from studies of oral, subcutaneous, or intraperitoneal (i.p.) administration of benzyl acetate to rats (reviewed in Adams *et al*., 2005 and JECFA, 1996).

4.3.2 Derivation of a CSAF for Interspecies Pharmacokinetic Differences (PK_{inter}CSAF)

Studies that report pharmacokinetic data for benzoic acid and sodium benzoate in humans and rats reported several quantitative parameters, such as AUC and C_{max}, that are suitable for deriving a CSAF to account for interspecies variability in pharmacokinetics (PK_{inter}CSAF). We selected the AUC as the primary kinetic parameter, as opposed to C_{max}, because we are concerned with potential adverse effects arising from chronic exposure, and because there is generally greater variability in AUCs than in C_{max} values, leading to a more conservative assessment (IPCS, 2005). For both the human and animal data discussed below, we present AUCs and dose-normalized AUCs (*i.e.*, AUC/Dose).

To derive the PK_{inter}CSAF, we used data from i.v. exposures to sodium benzoate in humans and rats, because pharmacokinetic data from oral exposure are not available in rats. Also, oral absorption is rapid and almost complete in both humans and rats. JECFA identified the POD from a chronic oral study of rats, so this approach is likely conservative – oral exposure to sodium benzoate yields a slightly lower internal dose compared to i.v. administration, because absorption in the digestive tract may not reach 100%.

Two i.v. human pharmacokinetic studies were identified, from which an AUC for plasma benzoate could be derived (*i.e.*, the US FDA pharmacokinetic studies of Ammonul administered to healthy adults; US FDA, 2004a). The administered i.v. dose of sodium benzoate was converted to an internal benzoic acid equivalent dose for each group in each study, and then the dose-normalized AUCs were calculated (Table 4.2).

Table 4.2 Internal Benzoic Acid Equivalent Doses and Areas Under the Curve for Humans After Intravenous Administration of Sodium Benzoate

Number of Subjects	Administered i.v. Dose (g/m^2)	BAED[a] (mg/kg bw)	AUC (µg*h/mL) Mean (SD)	AUC/BAED Mean (SD)	Reference
6	1	22.9	20.3 (3.6)	0.9 (0.2)	US FDA (2004a)[b]
6	2	45.8	114.9 (31.3)	2.5 (0.7)	US FDA (2004a)[b]
6	4	91.6	562.8 (142.3)	6.1 (1.6)	US FDA (2004a)[b]
17	3.75	85.9	564.6 (103.9)	6.6 (1.2)	US FDA (2004a)[c]
3	5.5	126.0	1,599.1 (463.1)	12.6 (3.6)	US FDA (2004a)[c]

Notes:
AUC = Area Under the Curve; BAED = Benzoic Acid Equivalent Dose; i.v. = Intravenous; SD = Standard Deviation; US FDA = United States Food and Drug Administration.
Shaded rows indicate the groups used in the AUC comparison in Table 4.4.
(a) Calculated internal sodium benzoate doses from reported i.v. doses with a conversion factor (k_m) of 37 to convert doses units of mg/m^2 to mg/kg bw for adult humans (US FDA, 2005). Converted sodium benzoate to benzoic acid equivalent doses based on the molecular masses of sodium benzoate (144.11 g/mol) and benzoic acid (122.123 g/mol).
(b) US FDA Study 973600.
(c) US FDA Study 951603.

The animal pharmacokinetic study by Gregus *et al*. (1992) was the only study in rats with sufficient quantitative pharmacokinetic data with which to calculate the AUCs for plasma benzoate. As with the human data, we converted administered i.v. doses of sodium benzoate in rats to internal benzoic acid equivalent doses. In addition, we further converted these doses to toxicologically equivalent doses in humans (*i.e.*, human equivalent doses [HEDs]) to account for inherent metabolic differences due to different body sizes, using the generally accepted allometric scaling method of body weight scaling to the ¾ power[10] (US EPA, 2011a; Rhomberg and Lewandowski, 2006). We then calculated dose-normalized AUCs by dividing the AUCs by the HEDs (Table 4.3).

[10] As per United States Environmental Protection Agency (US EPA, 2011a) guidance: HED = Dose (mg) × $(BWh/BWa)^{3/4}$, where BWh = 60 kg, the default adult human body weight, and BWa = 0.3 kg, the average rat body weight as reported in Gregus *et al*. (1992).

Table 4.3 Benzoic Acid Equivalent Doses, Body Weight-scaled Human Equivalent Doses, and Areas Under the Curve for Rats After Intravenous Administration of Sodium Benzoate

Number of Rats	Administered i.v. Dose (mmol/kg)	BAED[a] (mg/kg bw)	HED[b] (mg/kg bw)	AUC[c] (µg*h/mL) Mean (SD)	AUC/HED Mean (SD)	Reference
5-8	0.2	24.4	6.5	10.4 (0.8)	1.6 (0.1)	Gregus *et al.* (1992)
5-8	0.5	61.1	16.2	58.2 (6.3)	3.6 (0.4)	Gregus *et al.* (1992)
5-8	1	122.1	32.5	239.5 (22.5)	7.4 (0.7)	Gregus *et al.* (1992)
5-8	2	244.2	64.9	1,100.2 (89.2)	16.9 (1.4)	Gregus *et al.* (1992)

Notes:
AUC = Area Under the Curve; BAED = Benzoic Acid Equivalent Dose; bw/BW = Body Weight; HED = Human Equivalent Dose; i.v. = Intravenous; SD = Standard Deviation.
Shaded rows indicate the groups used in the AUC comparison in Table 4.4.
(a) Converted from mmol/kg bw to mg/kg bw based on the molecular mass of benzoic acid (122.123 g/mol).
(b) Converted to HEDs based on allometric scaling of $BW^{3/4}$ (US EPA, 2011a; Rhomberg and Lewandowski, 2006).
(c) Calculated based on the formula: AUC = F*Dose/CL, where F = Fraction absorbed (1 for i.v. administration) and CL = Clearance (in units of mL/kg*min) (Shen, 2013).

Converting the rat doses to HEDs is particularly important for this analysis, because there is a non-linear relationship between administered dose and AUC, with greater-than-proportional increases in AUCs with increasing benzoate doses in humans and rats. This is illustrated by the dose-normalized AUCs presented in Tables 4.2 and 4.3, which are not constant even after they are adjusted for dose (constant AUCs would be expected for substances with linear elimination kinetics). Dose-normalized AUCs are useful to compare across studies in which the specific study doses are not identical, although when there are apparent non-linearities in metabolism (as appears to be the case here), doses should be as close as possible prior to normalization. Therefore, we selected dose-normalized AUCs at comparable internal doses of benzoic acid from the US FDA human studies (US FDA, 2004a) and the rat study (Gregus *et al*., 1992) to calculate the ratios of human and rat dose-normalized AUCs (Table 4.4).

Table 4.4 Comparison of Dose-normalized AUCs from Intravenous Administration of Sodium Benzoate in Humans (US FDA, 2004a) and Rats (Gregus *et al*., 1992)

BAED in Humans[a] (mg/kg bw)	HED in Rats[b] (mg/kg bw)	Mean AUC_{Norm} in Humans (µg*h/mL)	Mean AUC_{Norm} in Rats (µg*h/mL)	Human AUC_{Norm}/Rat AUC_{Norm}
22.9	16.2	0.9	3.6	0.3
45.8	32.5	2.5	7.4	0.3
85.9	64.9	6.6	16.9	0.4

Notes:
AUC_{Norm} = Dose-normalized Area Under the Curve; BAED = Benzoic Acid Equivalent Dose; bw/BW = Body Weight; HED = Human Equivalent Dose.
(a) Converted to benzoic acid equivalent doses.
(b) Converted to human equivalent doses by scaling the rat internal benzoic acid equivalent doses by $BW^{3/4}$ (US EPA, 2011a; Rhomberg and Lewandowski, 2006).

The interspecies pharmacokinetic UF default value of 4 is meant to address two different concepts: the known differences across species that are due to differences in basal rates of metabolism (*i.e.*, rodents eliminate compounds faster than humans) and *unusual and unanticipated* differences when humans are more sensitive than rodents even beyond the understood differences in metabolism (*e.g.*, due to differences in metabolic pathways or enzyme efficiencies). Scaling the doses in rats to human equivalent doses according to the ¾ power of body weight addresses known interspecies differences in metabolism (Rhomberg and Lewandowski, 2006). Potential unusual and unanticipated differences in interspecies metabolism can only be identified by evaluating the concentration-time profiles after administration of

similar doses across species. If rodent doses are adjusted to human equivalent doses (by scaling dose to the ¾ power of body weight), and pharmacokinetic markers (*e.g.*, the AUC) are the same (*e.g.*, human AUC/rodent AUC ≈ 1), then it can be concluded that there are no unusual or unanticipated differences in metabolic pathways and that the only interspecies difference is due to the known metabolic differences related to body size. If the ratio of the rodent to human pharmacokinetic markers is less than 1 (*e.g.*, human AUC/rodent AUC < 1), then the traditional ¾ power body weight scaling is overly conservative, and humans are likely to have better metabolic capacity than rodents (*i.e.*, the UF should be less than 4).

The ratios of the human to rat dose-normalized AUCs range between 0.3-0.4, indicating that for the same adjusted dose (adjusted to account for basal differences in metabolism), rats are exposed to a higher internal dose of benzoic acid. Moreover, because the ratio of AUC across species is less than 1, it appears that the default pharmacokinetic UF of 4 is excessive. Because dietary exposures to benzoic acid and its salts for most individuals are at the low end of the range of the human dose studies (which were studies of pharmaceutical effects), we applied the ratio of 0.3 to the default pharmacokinetic UF of 4. The resulting PK_{inter}CSAF for benzoic acid and its salts is 1.2 (*i.e.*, the default value of 4 multiplied by the dose-normalized AUC ratio of 0.3). Although this CSAF was derived based on a small number of available studies, it is consistent with the qualitative analysis discussed in Section 4.3.1 and summarized in Table 4.1, which showed that the ADME of benzoic acid and its salts are very similar in humans and rats.

4.4 Comparison of Age-related Differences in Pharmacokinetics of Benzoic Acid and Its Salts

4.4.1 Qualitative Comparison

The available pharmacokinetic studies indicate that ADME patterns are generally similar in children and adults (see Section 4.1). For example, US FDA (2004b) noted that peak plasma benzoate levels from seven children (aged 3-26 months) following administration of 250-500 mg/kg bw of sodium benzoate (equivalent to 212-424 mg/kg bw of benzoic acid) for 1-2 hours were qualitatively similar to those in adults.

Neonates and infants may have a more limited capacity to metabolize benzoates compared to adults and children older than 1 year of age. Some studies reported reduced glycine conjugation capacity in neonates after i.v. exposure to benzoate (reviewed in Dorne *et al*., 2005), while other studies reported capacities in neonates after oral exposure that are similar to those of adults (Gow *et al*., 2001). The wide variability of benzoate metabolism in infants and neonates may be attributable to immaturity of the acylation system in the liver and kidneys (Batshaw *et al*., 2001), because mitochondrial glycine N-acyltransferase activity in the liver varied from 5-40% of peak activity between birth and 7 months of age, and peak activity was observed by 18 months of age (Mawal *et al*., 1997, as reviewed in Batshaw *et al*., 2001).

Some studies report older children (*i.e.*, 1 year of age or older) have higher rates of metabolic clearance compared to healthy adults for a number of metabolic pathways, including for glycine conjugation (*e.g.*, Dorne *et al*., 2005), but other studies report no significant differences among the mean rate of glycine conjugation in children, healthy adults, or the elderly[11] (*e.g.*, Dorne *et al*., 2004; reviewed in

[11] Dorne *et al*. (2004) stratified the age groups as follows: neonates (<1 month old), infants (>1 month to <1 year old), children (>1 to <16 years old), healthy adults (16 to <70 years old), and elderly (healthy adults >70 years old).

Badenhorst *et al*., 2013). The latter finding is supported by evidence indicating that adult-level kidney filtration rates (and thus typical clearance rates as well) are achieved by approximately 7 months of age in humans (Besunder *et al*., 1988).

Further, Dorne *et al*. (2005) analyzed metabolic pathway-related UFs for a number of compounds. They determined that the UFs for the pharmacokinetic component of intraspecies variability for glycine conjugation pathway were consistently less than the default value of 3.16 for children, younger adults, and older adults. Specifically, they reported that the 99th percentile UFs for adults and children were 1.6 and 1.8, respectively.[12]

Taken together, the evidence indicates that the metabolic capacity for benzoate may be limited in neonates because of their immature acylation systems, but human variability in benzoate pharmacokinetics is negligible after the age of 1 year.

4.4.2 Derivation of a CSAF for Intraspecies Pharmacokinetic Differences (PK_{intra}CSAF)

Similar to the PK_{inter}CSAF, we derived a CSAF for human variability in pharmacokinetics (PK_{intra}CSAF) using dose-normalized AUCs in humans after i.v. exposure to sodium benzoate. For healthy adults, we again relied on the US FDA studies (US FDA, 2004a) because they were the only studies that reported AUCs for plasma benzoate for several dose groups. Quantitative pharmacokinetic data in children are generally limited to those with severe genetic defects in urea synthesis. Because the therapeutic effect of sodium benzoate is mediated by its normal metabolic process, we determined that children with inborn errors of urea synthesis represent healthy children in the general population with regard to benzoate pharmacokinetics. We calculated AUCs from three clinical studies of neonates, infants, and children that reported time course plots of plasma benzoate (Green *et al*., 1983; Brusilow *et al*., 1984; Simell *et al*., 1986), because these were the only studies of children from which AUCs could be derived. We converted the administered doses of sodium benzoate to benzoic acid equivalent doses, and calculated the dose-normalized AUCs by dividing the AUCs by the benzoic acid equivalent doses (Table 4.5).

[12] This analysis was based on data from various substrates that undergo glycine conjugation and is not specific to benzoate.

Table 4.5 Benzoic Acid Equivalent Doses and Areas Under the Curve for Healthy Adults and Children with Inborn Errors of Urea Synthesis After Intravenous Administration of Sodium Benzoate

Subject (Age)	Number of Subjects	Administered i.v. Dose	BAED[a] (mg/kg bw)	AUC (µg*h/mL) Mean (SD)	AUC/BAED Mean (SD)	Reference
Adults (age not reported)	6	1 g/m^2	22.9[b]	20.3 (3.6)	0.9 (0.2)	US FDA (2004a)[c]
	6	2 g/m^2	45.8[b]	114.9 (31.3)	2.5 (0.7)	US FDA (2004a)[c]
	6	4 g/m^2	91.6[b]	562.8 (142.3)	6.1 (1.6)	US FDA (2004a)[c]
	17	3.75 g/m^2	85.9[b]	564.6 (103.9)	6.6 (1.2)	US FDA (2004a)[d]
	3	5.5 g/m^2	126.0[b]	1,599.1 (463.1)	12.6 (3.6)	US FDA (2004a)[d]
Neonates (3-7 days)	4	3.5 mmol/kg	105.9[e]	1,765[f] (107.7)	16.7 (1.0)	Green *et al*. (1983)
Infants (5-12 months)	2	250 mg/kg	211.9	2,319.2[g] (1,387.1)	10.9 (6.5)	Brusilow *et al*. (1984)
Children (2.8-12.6 years)	5	2 mmol/kg	244.2[c]	2,133.9[g] (218.9)	8.7 (0.9)	Simell *et al*. (1986)

Notes:
AUC = Area Under the Curve; BAED = Benzoic Acid Equivalent Dose; bw = Body Weight; i.v. = Intravenous; SD = Standard Deviation; US FDA = United States Food and Drug Administration.
Shaded rows indicate the groups used in the AUC comparison in Table 4.6.
(a) Converted to benzoic acid equivalent dose based on the molecular masses of sodium benzoate (144.11 g/mol) and benzoic acid (122.123 g/mol).
(b) Converted from reported i.v. doses using a conversion factor (k_m) of 37 to convert doses units of mg/m^2 to mg/kg bw for adult humans (US FDA, 2005).
(c) US FDA Study 973600.
(d) US FDA Study 951603.
(e) Converted from mmol/kg bw based on the molecular mass of benzoic acid (122.123 g/mol).
(f) Calculated based on the formula: AUC = F*Dose/CL, where F = Fraction absorbed (1 for i.v. administration) and CL = Clearance (in units of mL/kg bw*min) (Shen, 2013).
(g) Calculated from time course plots of plasma benzoate concentrations.

As discussed above, neonates and infants (*i.e.*, children younger than 1 year old) may have a limited capacity to metabolize benzoate because they have immature acylation systems in their liver and kidneys. As reviewed by Batshaw *et al*. (2001), the neonates in Green *et al*. (1983) had impaired renal function and clearance as well as limited benzoate conjugation capacity, due to their poor health status. The two infants in Brusilow *et al*. (1984) were also significantly health-compromised. The levels given are quite large compared to potential dietary intake. Healthy neonates and infants in the general population have little, if any, potential dietary exposure to added benzoic acid or its salts, so their lower metabolizing rates should not substantially contribute to uncertainties in deriving the ADI for benzoic acid and its salts. Also, the JECFA dietary assessment for benzoate did not include children younger than 1 year old (JECFA, 2015). For these reasons, we excluded the two studies in neonates and infants from our analysis (Green *et al*., 1983; Brusilow *et al*., 1984).

Instead, we relied on the study by Simell *et al*. (1986), which evaluated children older than 1 year of age with inborn errors of urea synthesis, to derive the $PK_{intra}CSAF$. As discussed above, these children likely did not differ from healthy children in the general population with regard to their capacity to metabolize benzoates. Simell *et al*. (1986) evaluated five children, ranging from 2.8-12.6 years old. Despite the relatively small sample size and wide age range, there was not significant variability in the dose-normalized AUCs, as evidenced by the small standard deviation, so we considered the pharmacokinetic data in Simell *et al*. (1986) to be robust.

While it is preferable to compare AUCs at similar administered doses, the doses in children were considerably higher than those in adults. Therefore, we selected the highest three dose groups in adults from the US FDA studies (US FDA, 2004a) and calculated a range of dose-normalized AUC ratios (Table 4.6).

Table 4.6 Comparison of Dose-normalized AUCs from Intravenous Data in Adults (US FDA, 2004a) and Children (Simell *et al.*, 1986)

BAED[a] in Adults (mg/kg bw)	BAED in Children (mg/kg bw)	Mean AUC_{Norm} in Adults (µg*h/mL)	Mean AUC_{Norm} in Children (µg*h/mL)	Child AUC_{Norm}/Adult AUC_{Norm}
91.6	244.2	6.1[b]	8.7[d]	1.4
85.9		6.6[c]		1.3
126.0		12.6[c]		0.7

Notes:
AUC_{Norm} = Dose-normalized Area Under the Curve; BAED = Benzoic Acid Equivalent Dose; bw =Body Weight; i.v. = Intravenous; US FDA = United States Food and Drug Administration.
(a) Converted from reported i.v. doses using a conversion factor (k_m) of 37 to convert doses units of mg/m^2 to mg/kg bw for adult humans (US FDA, 2005).
(b) US FDA Study 973600.
(c) US FDA Study 951603.
(d) Simell *et al*. (1986).

The child-adult ratios of dose-normalized AUCs ranged from 0.7-1.4, with a slight decreasing trend with increasing adult benzoic acid equivalent dose; thus, 1.4 serves as a conservative estimate of $PK_{intra}CSAF$ for deriving the benzoate ADI. That is, the pharmacokinetic component for human variability should be reduced from the default value of 3.16 to 1.4. This conclusion is consistent with that of our qualitative evaluation: that the ADME patterns of benzoic acid and its salts are similar between children and adults, and that in general, the clearance rates of several important metabolic processes, including glycine conjugation and kidney filtration, are comparable or higher in children than in adults.

5 Clinical Data in Humans

In Section 4, we discussed human pharmacokinetic data for benzoic acid and its salts. In this section, we discuss adverse effects reported in clinical studies of sodium benzoate treatment to address the toxicodynamic UF. We found that adverse effects are observed only at doses similar to or higher than the animal NOAEL. Because these studies were not designed specifically to focus on adverse effects, they do not provide strong enough evidence to support specific UFs for interspecies and intraspecies (human) variability in toxicodynamics. However, the results of these studies indicate that the UFs could be lower than the default values, and that, because of this, the ADI can be considered conservative.

Studies in humans and laboratory animals demonstrate that benzoate metabolism to hippurate by glycine conjugation in the liver and excretion in urine diverts nitrogen from urea production, and thus provides an alternative pathway for the elimination of waste nitrogen (Tremblay and Qureshi, 1993). Because of this, sodium benzoate has been used as a therapeutic agent to treat hyperammonemia (Tremblay and Qureshi, 1993). Sodium benzoate also inhibits D-amino acid oxidase, a flavoenzyme of peroxisomes in the central nervous system, *via* benzoyl CoA, the common intermediate to hippuric acid for benzoate. Therefore, it has been tested as a treatment for certain neuropsychological conditions (Lane *et al*., 2013). A number of clinical studies are available on the efficacy and potential adverse effects of sodium benzoate treatment for these conditions.

It is unclear why these clinical studies were not considered in previous safety assessments of benzoic acid and its salts in food or in the derivation of the ADI. However, the 2009 EHC 240 risk assessment guidelines encourage the use of human studies to inform hazard identification and risk characterization, and these studies are informative with regard to oral exposure (IPCS, 2009). Thus, we conducted online literature searches in PubMed, Scopus, and the US National Institutes of Health (NIH) clinical trials database to identify clinical studies of sodium benzoate. We only considered studies with doses higher than the current ADI and evaluated whether there were adverse effects at these higher levels. These studies are presented in Table 5.1 and briefly discussed below.

Trijbels *et al*. (1974) and Batshaw *et al*. (1981, 1982) were among the first clinicians to report observations from long-term sodium benzoate treatment in children with non-ketotic hyperglycinemia or inborn errors of urea synthesis. Twenty-nine infants and small children (aged 1-42 months) were treated with 100-300 mg/kg bw-day of sodium benzoate (equivalent to 84.7-254.2 mg/kg bw-day of benzoic acid) for 7 months to 3 years. The therapeutic doses were effective at maintaining normal plasma ammonia concentrations and were well tolerated. One adverse event was reported when a child was accidentally given a dose of 792 mg/kg bw-day of sodium benzoate (equivalent to 671.1 mg/kg bw-day of benzoic acid) for 2 days and became irritable and vomited. These symptoms resolved within 12 hours of discontinuing the drug, and hepatic and renal functions and electrolyte balance all remained normal. Two other children experienced vomiting and irritation after accidental exposures to 800 mg/kg bw-day of sodium benzoate (equivalent to 677.9 mg/kg bw-day of benzoic acid); these symptoms ceased once the drug was discontinued.

A number of additional case reports of children with inborn errors of urea synthesis also reported that sodium benzoate therapy (either alone or in combination with protein restriction, L-carnitine supplementation, sodium phenylacetate, or sodium phenylbutyrate) is effective at improving survival and ammonia nitrogen removal (Brubakk *et al.*, 1982; Mizutani *et al.*, 1983; Takeda *et al.*, 1983; Qureshi *et al.*, 1984; Van de Bor *et al.*, 1984; Letarte *et al.*, 1985; McCormick *et al.*, 1985; Walter *et al.*, 1992;

Maestri *et al.*, 1996). These children, including neonates, were treated with sodium benzoate at 200-500 mg/kg bw-day (equivalent to 169.5-423.7 mg/kg bw-day of benzoic acid, or 34-85 times the current ADI) for several weeks to several years and did not experience any notable adverse events that were related to the treatment. One case report indicated that a 9-month treatment with 410 mg/kg bw-day of sodium benzoate (equivalent to 347.4 mg/kg bw-day of benzoic acid) in a 33-year-old woman was effective at maintaining normal plasma ammonia concentrations and well tolerated without any adverse effects (Call *et al.*, 1984).

One clinical study compared the effects of sodium benzoate treatment in combination with protein restriction and carnitine supplementation to those of protein restriction alone in children with inborn errors of urea synthesis (Feoli-Fonseca *et al*., 1996). Add-on treatments of sodium benzoate at average doses of 102 and 69 mg/kg bw-day (equivalent to 86.4 and 58.5 mg/kg bw-day of benzoic acid) for 2-98 months in 11 children were not associated with any adverse effects.

Sodium benzoate has also been evaluated as a therapeutic agent for acute hyperammonemia in neonates, children, and adults. A number of case reports and case series indicated that sodium benzoate, either alone or in combination with sodium phenylacetate, was effective in improving survival (Brusilow *et al.*, 1979, 1980; Batshaw and Brusilow, 1980; Kodama *et al.*, 1981; Brusilow *et al.*, 1984; Watson *et al.*, 1985; Sharp and Lang, 1987; Sakuma *et al.*, 1992; Tuchman *et al.*, 1992; Enns *et al.*, 2007). The doses of sodium benzoate ranged from approximately 90-500 mg/kg bw-day (equivalent to 76.3-423.7 mg/kg bw-day of benzoic acid) and the duration of the treatment usually only lasted from 24 hours to a few days. No treatment-related adverse effects were reported.

In addition to hyperammonemia, sodium benzoate has been used in several intervention studies, including two randomized controlled trials (RCTs), for treating patients with chronic or acute hepatic encephalopathy (Mendenhall *et al*., 1986; Uribe *et al*., 1990; Sushma *et al*., 1992). Patients were randomized to either standard therapy for hepatic encephalopathy or approximately 80-140 mg/kg bw-day of sodium benzoate, equivalent to 67.8-118.6 mg/kg bw-day of benzoic acid, that lasted from several days to a few weeks. Sodium benzoate treatments in 58 patients were shown to be an effective treatment for hepatic encephalopathy, and no treatment-related adverse events were observed in these studies. In Sushma *et al*. (1992), some patients who received sodium benzoate experienced some gastrointestinal symptoms, including vomiting and nausea, but these symptoms did not respond to a reduction in the dosage of sodium benzoate, suggesting they were not treatment-related, and were controlled by the administration of ranitidine.

Most recently, sodium benzoate was explored as a potential therapeutic agent for neuropsychological conditions such as chronic schizophrenia and Alzheimer's disease in two RCTs of Asian populations (Lane *et al*., 2013; Lin *et al*., 2014). These studies indicated that sodium benzoate treatments in 55 patients for 6-24 weeks were effective in treating and managing these two conditions, and no adverse events were observed. The doses of sodium benzoate used in these trials, ranging from approximately 3.6-14.6 mg/kg bw-day (equivalent to 3.1-12.4 mg/kg bw-day of benzoic acid), were considerably lower than those in previous clinical studies and comparable to the current ADI.

Together, these clinical studies demonstrate that sodium benzoate treatment at doses up to 500 mg/kg bw-day (equivalent to 423.7 mg/kg bw-day of benzoic acid, or 85 times the current ADI) are well tolerated in humans of all ages, with no apparent adverse effects. Observed toxicity, such as vomiting and irritation, occurred at doses around 800 mg/kg bw-day and was transient and reversible once the exposure was discontinued. The highest human NOAEL (423.7 mg/kg bw-day benzoic acid equivalent) and LOAEL (677.9 mg/kg bw-day benzoic acid equivalent) of sodium benzoate, as suggested by these clinical data, are comparable to the rodent NOAEL of 500 mg/kg bw-day of benzoic acid identified from animal

toxicity studies, thus providing supporting evidence that the UF for interspecies differences in toxicodynamics should be reduced or possibly eliminated.

Also, because a therapeutic use of sodium benzoate is to treat genetic disorders of urea synthesis, the recipients of treatment are generally children – the population of interest in the most recent JECFA assessment on benzoic acid and its salts. The therapeutic doses are generally higher and the treatment durations are often longer in children than in adults. The clinical reports did not show that children are more sensitive to the effects of sodium benzoate. Furthermore, the liver is the main organ that metabolizes benzoic acid, so one could argue that individuals with impaired liver function may be a sensitive population to the potential toxic effects of sodium benzoate. However, clinical intervention studies conducted in patients with liver dysfunction showed that there were no treatment-related adverse effects from doses of 5-10 g/day of sodium benzoate, equivalent to approximately 70-140 mg/kg bw-day of benzoic acid. Observed NOAELs in children with urea cycle defects and in individuals with impaired liver functions are similar and are at least one order of magnitude higher than the current ADI of 5 mg/kg bw-day, indicating that benzoate exposures at levels considerably higher than the current ADI do not pose any health risk to potentially sensitive populations.

Collectively, this evidence supports the UF for human variability in toxicodynamics being reduced, but the specific UF cannot be determined based on these data.

Table 5.1 Characteristics of Clinical Studies of Sodium Benzoate

Study	Study Design	Study Population (Age)	Patient Condition	N of Patients Treated	Treatment	BAED[a] (mg/kg bw-day)	Treatment Duration	Primary Outcome	Treatment Successful?	Adverse Events[b]
Trijbels *et al.* (1974)	CR	Female infant (1 month)	Non-ketotic hyperglycinemia	1	NaB	84.7-254.2	3 years	Amino acids analyses, plasma ammonia	Yes	None
Brusilow *et al.* (1979, 1980)	CR	Female (16 years)	Inborn errors of urea synthesis	1	NaB	132.2[c]	10 days	Plasma ammonia, urinary nitrogen	Yes	None
Brusilow *et al.* (1980)	CS	Children (11 months-18 years)	Hyperammonemic coma	4	NaB	169.5-296.6	24 hours	Plasma ammonia	Yes	None
Batshaw and Brusilow (1980)	CS	Children (1 month-17 years)	Inborn errors of urea synthesis	7	NaB	211.9-423.7	24 hours	Plasma ammonia	Yes	None
Batshaw *et al.* (1981)	CS	Infants (1-6 months)	Inborn errors of urea synthesis	2	NaB	213.7-244.2[d]	8-20 months	Plasma ammonia	Yes	None[e]
Kodama *et al.* (1981)	CR	Female child (8 years)	Inborn errors of urea synthesis	1	NaB	79.7[f]	24 hours	Plasma ammonia	Yes	None
Batshaw *et al.* (1982)	CS	Infants (7-42 months)	Inborn errors of urea synthesis	26	NaB	211.9	7-62 months	Hyperammonemia episode, growth	Yes	None[g]
Brubakk *et al.* (1982)	CR	Male neonate (2 hours)	Inborn errors of urea synthesis	1	NaB	211.9	4 months	Plasma ammonia	Yes	None
Mizutani *et al.* (1983)	CR	Male child (4.6 years)	Inborn errors of urea synthesis	1	NaB + PA	211.9	9 weeks	Plasma ammonia	Yes	None
Takeda *et al.* (1983)	CR	Girl (8 years)	Inborn errors of urea synthesis	1	NaB	169.5	13 months	Plasma ammonia	Yes	None
Brusilow *et al.* (1984)	CS	Children (1-26 months)	Inborn errors of urea synthesis	7	NaB + NaP	211.9-423.7	24 hours	Plasma ammonia	Yes	None
Call *et al.* (1984)	CR	Woman (33 years)	Inborn errors of urea synthesis	1	NaB	347.4	9 months	Plasma ammonia	Yes	None
Qureshi *et al.* (1984)	CR	Female (15 years)	Inborn errors of urea synthesis	1	NaB	211.9-317.8	9 months	Plasma ammonia, urinary nitrogen	Yes	None
Van de Bor *et al.* (1984)	CR	Female infant (7 months)	Inborn errors of urea synthesis	1	NaB + NaP	211.9	8 months	Growth	Yes	None

Study	Study Design	Study Population (Age)	Patient Condition	N of Patients Treated	Treatment	BAED[a] (mg/kg bw-day)	Treatment Duration	Primary Outcome	Treatment Successful?	Adverse Events[b]
Letarte *et al.* (1985)	CR	Male child (46 months)	Inborn errors of urea synthesis	1	NaB	211.9	3 years	Growth, plasma and urinary nitrogen	Yes	None
McCormick *et al.* (1985)	CR	Neonate (2 days)	Inborn errors of urea synthesis	1	NaB	211.9	6 months	Plasma ammonia	Yes	None
Watson *et al.* (1985)	CS	Adults (23-47 years)	Hyperammonemia secondary to leukemia	1	NaB + NaP	105.8-211.6[h]	3 days	Plasma ammonia	Yes	None
Sharp and Lang (1987)	CR	Man (57 years)	Hyperammonemia secondary to leukemia	1	NaB	211.6[h]	1 day	Plasma ammonia	Yes	None
Sakuma *et al.* (1992)	CS	Neonates (7-33 hours)	Transient hyperammonemia	2	NaB	169.5	1 day	Urinary nitrogen	Yes	None
Tuchman *et al.* (1992)	CS	Neonates (5-79 hours)	Inborn errors of urea synthesis	2	NaB + NaP	211.9	4-7 days	Plasma ammonia	Yes	None
Walter *et al.* (1992)	CR	Male neonate (4 days)	Inborn errors of urea synthesis	1	NaB	423.7	3 weeks	Plasma ammonia	Yes	None
Feoli-Fonseca *et al.* (1996)	CS	Children (0.9-23.5 years)	Inborn errors of urea synthesis	11	A: NaB + PR B: NaB + PR + Carnitine	A: 86.4 ± 24.2 B: 58.5 ± 17.1[i]	2-98 months	Carnitine metabolism and ammonia nitrogen removal	No	None
Maestri *et al.* (1996)	CS	Female children (1-17 years)	Inborn errors of urea synthesis	A: 11 B: 22	A: NaB B: NaB + NaP + NaPB	211.9	A: 3.2 years[j] B: 3.7 years[j]	Survival, hyperammonemic episodes, cognitive measurements	Yes	None
Enns *et al.* (2007)	CS	Neonates, children, adults	Hyperammonemia from urea-cycle defect	299	NaB + NaP	A: 211.9[k] B: 126.3[l]	24 hours	Survival of the episode of hyperammonemia	Yes	None
Mendenhall *et al.* (1986)	INT	Adults (mean age: 64 years)	Portal systemic encephalopathy	8	NaB + NaP	141.4[h]	7 days	Portal systemic encephalopathy index	Yes	None

Study	Study Design	Study Population (Age)	Patient Condition	N of Patients Treated	Treatment	BAED[a] (mg/kg bw-day)	Treatment Duration	Primary Outcome	Treatment Successful?	Adverse Events[b]
Uribe *et al.* (1990)	RCT	Adults (mean age: 58 years)	Portal systemic encephalopathy	12	NaB	79.1[h]	2 weeks	Portal systemic encephalopathy index	Yes	None
Sushma *et al.* (1992)	RCT	Adults (mean age: 35.6 years)	Acute hepatic encephalopathy	38	NaB	141.4[h]	11.6 days[m]	Survival, mental status, biochemical measures	Yes	None
Lane *et al.* (2013)	RCT	Adults (mean age: 37.3 years)	Chronic schizophrenia	25	NaB	12.4[n]	6 weeks	The Positive and Negative Syndrome Scale (PANSS) total score	Yes	None
Lin *et al.* (2014)	RCT	Adults (mean age: 70 years)	Amnestic mild cognitive impairment or mild Alzheimer's disease	30	NaB	3.6-10.6[h]	24 weeks	The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) score	Yes	None

Notes:

BAED = Benzoic Acid Equivalent Dose; bw = Body Weight; CR = Case Report; CS = Case Series; INT = Intervention Study; NaB = Sodium Benzoate; NaP = Sodium Phenylacetate; NaPB = Sodium Phenylburitate; PA = Phenylacetic Acid; PR = Protein Restriction; RCT = Randomized Controlled Trial.

(a) Presented as benzoic acid equivalent.

(b) Adverse events related to the sodium benzoate treatment.

(c) Converted from reported dose with the reported body weight of 40 kg.

(d) Converted from reported doses with the molecular mass of benzoic acid (122.123 g/mol).

(e) No adverse effects at 252-288 mg/kg bw-day; irritation and vomiting after accidental exposure to 793 mg/kg bw-day for 2 days.

(f) Converted from reported dose with the average body weight of 31.8 kg for children (6 to <11 years old) (US EPA, 2011b).

(g) No adverse effects at 250 mg/kg bw-day; irritation and vomiting after accidental exposure to 800 mg/kg bw-day.

(h) Converted from reported doses with the standard adult human body weight of 60 kg (IPCS, 2009).

(i) Converted from reported doses with the molecular mass of benzoic acid (122.123 g/mol) and the standard adult human body weight of 60 kg (IPCS, 2009).

(j) Average duration for each treatment protocol.

(k) A for infants and children (≤20 kg).

(l) B for children (>20 kg) and adults, converted from reported intravenous (i.v.) doses with a conversion factor (k_m) of 37 to convert dose units of mg/m^2 to mg/kg bw for adult humans (US FDA, 2005).

(m) Average duration for sodium benzoate treatment.

(n) Converted from reported dose with the reported average body weight of 68.6 kg for the treatment group.

6 Conclusions

In 2000, JECFA identified a group ADI of 0-5 mg/kg bw-day for benzoic acid, its salts, and precursor compounds based on a four-generation rat study conducted in 1960 with a NOAEL of 500 mg/kg bw-day, and a total UF of 100: 10 for interspecies variability and 10 for database uncertainty. Many studies on benzoic acid and its salts have been conducted since the ADI was first derived, including toxicity, pharmacokinetic, and clinical studies. It is striking that data from all these studies are consistent. Collectively, they support lowering the UFs for deriving the ADI for benzoic acid and its salts.

For example, the animal toxicity database for oral exposures to benzoic acid, its salts, and related precursor compounds is extensive, and includes acute and chronic toxicity, reproductive/developmental toxicity, carcinogenicity, and genotoxicity studies. These studies consistently report a lack of toxicity at doses up to 1,000 mg/kg bw-day. Human clinical data on sodium benzoate as a therapeutic agent provide additional evidence supporting the lack of toxicity at doses up to 500 mg/kg bw-day. This indicates that the UF for database uncertainty is not warranted and should be changed to 1.

The pharmacokinetics of sodium benzoate and benzoic acid are nearly identical in humans and rats. A quantitative comparisons of AUCs supports a CSAF of 1.2 for interspecies variability in pharmacokinetics (in place of the default value of 4). In addition, data from healthy adults and children with urea cycle defects support a CSAF of 1.4 for human variability in pharmacokinetics (in place of the default value of 3.16).

Clinical studies of sodium benzoate in children and adults support reducing the UFs for interspecies and intraspecies variability in toxicodynamics, but the data are not sufficient to derive specific CSAFs. Therefore toxicodynamic components of the UFs for interspecies and human variability should remain at their default values of 2.5 and 3.16, respectively, although we note that these default factors are conservative.

Taken as a whole, the current safety database clearly supports a total UF of 13: 1.2 for interspecies variability in pharmacokinetics, 1.4 for human variability in pharmacokinetics, 2.5 for interspecies variability in toxicodynamics, 3.16 for human variability in toxicodynamics, and 1 for database uncertainty, resulting in an ADI for benzoic acid and its salts of 0-38 mg/kg bw-day.

References

Adams, TB; Cohen, SM; Doull, J; Feron, VJ; Goodman, JI; Marnett, LJ; Munro, IC; Portoghese, PS; Smith, RL; Waddell, WJ; Wagner, BM. 2005. "The FEMA GRAS assessment of benzyl derivatives used as flavor ingredients." *Food Chem. Toxicol.* 43(8):1207-1240. doi: 10.1016/j.fct.2004.11.014.

Badenhorst, CP; van der Sluis, R; Erasmus, E; van Dijk, AA. 2013. "Glycine conjugation: Importance in metabolism, the role of glycine N-acyltransferase, and factors that influence interindividual variation." *Expert Opin. Drug Metab. Toxicol.* 9(9):1139-1153. doi: 10.1517/17425255.2013.796929.

Batshaw, ML; Brusilow, S; Waber, L; Blom, W; Brubakk, AM; Burton, BK; Cann, HM; Kerr, D; Mamunes, P; Matalon, R; Myerberg, D; Schafer, IA. 1982. "Treatment of inborn errors of urea synthesis: Activation of alternative pathways of waste nitrogen synthesis and excretion." *N. Engl. J. Med.* 306(23):1387-1392. doi: 10.1056/NEJM198206103062303.

Batshaw, ML; Brusilow, SW. 1980. "Treatment of hyperammonemic coma caused by inborn errors of urea synthesis." *J. Pediatr.* 97(6):893-900. doi: 10.1016/S0022-3476(80)80416-1.

Batshaw, ML; MacArthur, RB; Tuchman, M. 2001. "Alternative pathway therapy for urea cycle disorders: Twenty years later." *J. Pediatr.* 138(1 (Suppl.)):S46-S55. doi: 10.1067/mpd.2001.111836.

Batshaw, ML; Painter, MJ; Sproul, GT; Schafer, IA; Thomas, GH; Brusilow, S. 1981. "Therapy of urea cycle enzymopathies: Three case studies." *Johns Hopkins Med. J.* 148(1):34-40.

Besunder, JB; Reed, MD; Blumer, JL. 1988. "Principles of drug biodisposition in the neonate. A critical evaluation of the pharmacokinetic-pharmacodynamic interface (Part I)." *Clin. Pharmacokinet.* 14(4):189-216. doi: 10.2165/00003088-198814040-00001.

Bogen, KT. 2016. "Linear-no-threshold default assumptions for noncancer and nongenotoxic cancer risks: A mathematical and biological critique." *Risk Anal.* 36(3):589-604. doi: 10.1111/risa.12460.

Bolt, HM. 2003. "Genotoxicity--threshold or not? Introduction of cases of industrial chemicals." *Toxicol. Lett.* 140-141:43-51.

Bray, HG; Thorpe, WV; White, K. 1951. "Kinetic studies of the metabolism of foreign organic compounds. 1. The formation of benzoic acid from benzamide toluene, benzyl alcohol and benzaldehyde and its conjugation with glycine and glucuronic acid in the rabbit." *Biochem. J.* 48(1):88-96.

Bridges, JW; French, MR; Smith, RL; Williams, RT. 1970. "The fate of benzoic acid in various species." *Biochem. J.* 118(1):47-51. doi: 10.1042/bj1180047.

Brubakk, AM; Teijema, LL; Blom, W; Berger, R. 1982. "Successful treatment of severe OTC deficiency." *J. Pediatr.* 100(6):929-931. doi: 10.1016/S0022-3476(82)80518-0.

Brul, S; Coote, P. 1999. "Preservative agents in foods. Mode of action and microbial resistance mechanisms." *Int. J. Food Microbiol.* 50 (1-2) :1-17.

Brusilow, S; Tinker, J; Batshaw, ML. 1980. "Amino acid acylation: A mechanism of nitrogen excretion in inborn errors of urea synthesis." *Science* 207(4431):659-661. doi: 10.1126/science.6243418.

Brusilow, SW; Danney, M; Waber, LJ; Batshaw, M; Burton, B; Levitsky, L; Roth, K; McKeethren, C; Ward, J. 1984. "Treatment of episodic hyperammonemia in children with inborn errors of urea synthesis." *N. Engl. J. Med.* 310(25):1630-1634. doi: 10.1056/NEJM198406213102503.

Brusilow, SW; Valle, DL; Batshaw, M. 1979. "New pathways of nitrogen excretion in inborn errors of urea synthesis." *Lancet* 314(8140):452-454. doi: 10.1016/S0140-6736(79)91503-4.

Call, G; Seay, AR; Sherry, R; Qureshi, IA. 1984. "Clinical features of carbamyl phosphate synthetase-I deficiency in an adult." *Ann. Neurol.* 16(1):90-93. doi: 10.1002/ana.410160118.

Dorne, JL; Walton, K; Renwick, AG. 2004. "Human variability for metabolic pathways with limited data (CYP2A6, CYP2C9, CYP2E1, ADH, esterases, glycine and sulphate conjugation)." *Food Chem. Toxicol.* 42(3):397-421. doi: 10.1016/j.fct.2003.10.003.

Dorne, JL; Walton, K; Renwick, AG. 2005. "Human variability in xenobiotic metabolism and pathway-related uncertainty factors for chemical risk assessment: A review." *Food Chem. Toxicol.* 43(2):203-216. doi: 10.1016/j.fct.2004.05.011.

Enns, GM; Berry, SA; Berry, GT; Rhead, WJ; Brusilow, SW; Hamosh, A. 2007. "Survival after treatment with phenylacetate and benzoate for urea-cycle disorders." *N. Engl. J. Med.* 356(22):2282-2292. doi: 10.1056/NEJMoa066596.

European Food Safety Authority (EFSA). 2016. "Scientific Opinion on the re-evaluation of benzoic acid (E 210), sodium benzoate (E 211), potassium benzoate (E 212) and calcium benzoate (E 213) as food additives." Panel on Food Additives and Nutrient Sources (ANS). *EFSA J.* 14(3):4433. doi: 10.2903/j.efsa.2016.4433. 110p.

Federation of American Societies for Experimental Biology (FASEB). 1973. "Evaluation of the Health Aspects of Benzoic Acid and Sodium Benzoate as Food Ingredients." Life Sciences Research Office. Report to US Food and Drug Administration (US FDA). NTIS PB-223837; SCOGS-7. 24p., January.

Feoli-Fonseca, JC; Lambert, M; Mitchell, G; Melancon, SB; Dallaire, L; Millington, DS; Qureshi, IA. 1996. "Chronic sodium benzoate therapy in children with inborn errors of urea synthesis: Effect on carnitine metabolism and ammonia nitrogen removal." *Biochem. Mol. Med.* 57(1):31-36. doi: 10.1006/bmme.1996.0006.

Food Standards Australia New Zealand (FSANZ). 2016. "Sulphites." June. Accessed at http://www.foodstandards.gov.au/consumer/additives/sulphite/Pages/default.aspx.

Gow, PJ; Ghabrial, H; Smallwood, RA; Morgan, DJ; Ching, MS. 2001. "Neonatal hepatic drug elimination." *Pharmacol. Toxicol.* 88(1):3-15. doi: 10.1034/j.1600-0773.2001.088001003.x.

Green, TP; Marchessault, RP; Freese, DK. 1983. "Disposition of sodium benzoate in newborn infants with hyperammonemia." *J. Pediatr.* 102(5):785-790. doi: 10.1016/S0022-3476(83)80259-5.

Gregus, Z; Fekete, T; Varga, F; Klaassen, CD. 1992. "Availability of glycine and coenzyme A limits glycine conjugation in vivo." *Drug Metab. Dispos.* 20(2):234-240.

Greim, H; Albertini, RJ. 2012a. *The Cellular Response to the Genotoxic Insult: The Question of Threshold for Genotoxic Carcinogens.* Royal Society of Chemistry. 334p.

Greim, H; Albertini, RJ. 2012b. "Introduction and conclusion: The rationale for thresholds for genotoxic carcinogens." In *The Cellular Response to the Genotoxic Insult: The Question of Threshold for Genotoxic Carcinogens.* Royal Society of Chemistry. p1-20.

Informatics, Inc. 1972. "GRAS (Generally Recognized as Safe) Food Ingredients - Benzoic Acid and Sodium Benzoate." Report to US Food and Drug Administration (US FDA) NTIS PB-221208. Rockville, MD, 135p., September.

International Programme on Chemical Safety (IPCS). 2005. "Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration-Response Assessment." World Health Organization (WHO); International Labour Organisation; United Nations Environmental Programme. IPCS Harmonization Project Document No. 2. 100p. Accessed at http://www.who.int/ipcs/methods/harmonization/areas/uncertainty/en.

International Programme on Chemical Safety (IPCS). 2009. "Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food." United Nations Environmental Programme; International Labour Organisation; World Health Organization (WHO) Environmental Health Criteria 240. 731p. Accessed at http://www.who.int/foodsafety/publications/chemical-food/en.

Inter-Organization Programme for the Sound Management of Chemicals (IOMC). 2000. "Benzoic Acid and Sodium Benzoate." World Health Organization (WHO) Concise International Chemical Assessment Document (CICAD) 26. 52p. Accessed at http://www.who.int/ipcs/publications/cicad/cicad26_rev_1.pdf?ua=1.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1962. "Evaluation of the Toxicity of a Number of Antimicrobials and Antioxidants: Sixth Report of the Joint FAO/WHO Expert Committee on Food Additives." World Health Organization (WHO), Geneva, Switzerland, WHO Technical Report Series No. 228. 104p. Accessed at http://apps.who.int/iris/bitstream/10665/40518/1/WHO_TRS_228.pdf.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1996. "Toxicological Evaluation of Certain Food and Additives: Report of the Forty-Sixth Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)." World Health Organization (WHO), Geneva, Switzerland, WHO Food Additives Series 37. Accessed at http://www.inchem.org/documents/jecfa/jecmono/v37je01.htm.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1997. "Evaluation of Certain Food Additives and Contaminants. Forty-Sixth Report of the Joint FAO/WHO Expert Committee on Food Additives." World Health Organization (WHO), Geneva, Switzerland, WHO Technical Report Series 868. 80p. Accessed at http://apps.who.int/iris/bitstream/10665/41962/1/WHO_TRS_868.pdf.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2002. "Polychlorinated dibenzodioxins, polychlorinated dibenzofurans and coplanar polychlorinated biphenyls." WHO Technical Report Series 909. In *Evaluation of Certain Food Additives and Contaminants: Fifty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA).* World Health Organization (WHO), Geneva, Switzerland. p121-149. Accessed at http://apps.who.int/iris/bitstream/10665/42578/1/WHO_TRS_909.pdf.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2004. "Methylmercury." WHO Technical Report Series 922. In *Evaluation of Certain Food Additives and Contaminants: Sixty-first Report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA).* World Health Organization (WHO), Geneva, Switzerland. p132-143. Accessed at http://apps.who.int/iris/bitstream/10665/42849/1/WHO_TRS_922.pdf.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2015. "Safety Evaluation of Certain Food Additives and Contaminants: Prepared by the Eightieth Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)." World Health Organization (WHO), Geneva, Switzerland. WHO Food Additives Series 71. 142p.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2016. "Evaluation of Certain Food Additives and Contaminants: Eightieth Report of the Joint FAO/WHO Expert Committee on Food Additives." World Health Organization (WHO), Geneva, Switzerland, WHO Technical Report Series 995. 132p.

Kao, J; Jones, CA; Fry, JR; Bridges, JW. 1978. "Species differences in the metabolism of benzoic acid by isolated hepatocytes and kidney tubule fragments." *Life Sci.* 23(12):1221-1228. doi: 10.1016/0024-3205(78)90499-X.

Kieckebusch, W; Lang, K. 1960. "The tolerability of benzoic acid in chronic feeding experiments." *Arzneimittelforschung* 10:1001-1003.

Klaassen, CD; Watkins, JB III. 2003. *Casarett and Doull's Essentials of Toxicology.* McGraw-Hill, Inc. 533p.

Kodama, H; Nose, O; Tajiri, J; Maki, I; Sano, T; Harada, T; Kai, H; Yabuuchi, H. 1981. "Treatment with sodium benzoate in a patient with ornithine transcarbamylase deficiency." *Pediatr. Int.* 23(3):399. doi: 10.1111/j.1442-200X.1981.tb01658.x.

Kubota, K; Horai, Y; Kushida, K; Ishizaki, T. 1988. "Determination of benzoic acid and hippuric acid in human plasma and urine by high-performance liquid chromatography." *J. Chromatogr.* 425(1):67-75. doi: 10.1016/0378-4347(88)80007-0.

Kubota, K; Ishizaki, T. 1991. "Dose-dependent pharmacokinetics of benzoic acid following oral administration of sodium benzoate to humans." *Eur. J. Clin. Pharmacol.* 41(4):363-368. doi: 10.1007/BF00314969.

Lane, HY; Lin, CH; Green, MF; Hellemann, G; Huang, CC; Chen, PW; Tun, R; Chang, YC; Tsai, GE. 2013. "Add-on treatment of benzoate for schizophrenia: a randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor." *JAMA Psychiatry* 70(12):1267-1275. doi: 10.1001/jamapsychiatry.2013.2159.

Lennerz, BS; Vafai, SB; Delaney, NF; Clish, CB; Deik, AA; Pierce, KA; Ludwig, DS; Mootha, VK. 2015. "Effects of sodium benzoate, a widely used food preservative, on glucose homeostasis and metabolic profiles in humans." *Mol. Genet. Metab.* 114(1):73-79. doi: 10.1016/j.ymgme.2014.11.010.

Letarte, J; Ouellet, R; Qureshi, IA; Godard, M. 1985. "Chronic benzoate therapy in a boy with partial ornithine transcarbamylase deficiency." J. Pediatr. 106(5):794-797. doi: 10.1016/S0022-3476(85)80359-0.

Lin, CH; Chen, PK; Chang, YC; Chuo, LJ; Chen, YS; Tsai, GE; Lane, HY. 2014. "Benzoate, a D-amino acid oxidase inhibitor, for the treatment of early-phase Alzheimer disease: A randomized, double-blind, placebo-controlled trial." *Biol. Psychiatry* 75(9):678-685. doi: 10.1016/j.biopsych.2013.08.010.

Lutz, WK; Lutz, RW. 2009. "Statistical model to estimate a threshold dose and its confidence limits for the analysis of sublinear dose-response relationships, exemplified for mutagenicity data." *Mutat. Res.* 678(2):118-122.

MacArthur, RB; Altincatal, A; Tuchman, M. 2004. "Pharmacokinetics of sodium phenylacetate and sodium benzoate following intravenous administration as both a bolus and continuous infusion to healthy adult volunteers." *Mol. Genet. Metab.* 81(Suppl. 1):S67-S73. doi: 10.1016/j.ymgme.2003.12.011.

MacDermot, KD; Nelson, W; Soutter, V; Towne, D; Schulman, JD. 1981. "Glycine and benzoate conjugation and glycine acyltransferase activity in the developing and adult rat: Possible relationships to nonketotic hyperglycinemia." *Dev. Pharmacol. Ther.* 3(3):150-159.

Maestri, NE; Brusilow, SW; Clissold, DB; Bassett, SS. 1996. "Long-term treatment of girls with ornithine transcarbamylase deficiency." *N. Engl. J. Med.* 335(12):855-859.

McCormick, K; Viscardi, RM; Robinson, B; Heininger, J. 1985. "Partial pyruvate decarboxylase deficiency with profound lactic acidosis and hyperammonemia: Responses to dichloroacetate and benzoate." *Am. J. Med. Genet.* 22(2):291-299. doi: 10.1002/ajmg.1320220211.

Mendenhall, CL; Rouster, S; Marshall, L; Weesner, R. 1986. "A new therapy for portal systemic encephalopathy." *Am. J. Gastroenterol.* 81(7):540-543.

Mizutani, N; Maehara, M; Hayakawa, C; Kato, T; Watanabe, K; Suzuki, S. 1983. "Hyperargininemia: Clinical course and treatment with sodium benzoate and phenylacetic acid." *Brain Dev.* 5(6):555-563. doi: 10.1016/S0387-7604(83)80059-X.

Nair, B. 2001. "Final report on the safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate." *Int. J. Toxicol.* 20(Suppl. 3):23-50. doi: 10.1080/10915810152630729.

National Research Council (NRC). 1983. "Risk Assessment in the Federal Government: Managing the Process." Committee on the Institutional Means for Assessment of Risks to Public Health. National Academy Press, Washington, DC, 191p. Accessed at http://www.nap.edu/openbook.php?isbn=0309033497.

Organisation for Economic Co-operation and Development (OECD). 2001. "SIDS Initial Assessment Report for SIAM 13 on Benzoates: Benzoic Acid (CAS No. 65-85-0), Sodium Benzoate (CAS No. 532-32-1), Potassium Benzoate (CAS No. 582-25-2), and Benzyl Alcohol (CAS No. 100-51-6)." UNEP Publications. 320p.

Oyanagi, K; Kuniya, Y; Tsuchiyama, A; Nakao, T; Owada, E; Sato, J; Ito, K. 1987. "Nonlinear elimination of benzoate in patients with congenital hyperammonemia." *J. Pediatr.* 110(4):634-636. doi: 10.1016/S0022-3476(87)80568-1.

Qureshi, IA; Letarte, J; Ouellet, R; Batshaw, ML; Brusilow, S. 1984. "Treatment of hyperargininemia with sodium benzoate and arginine-restricted diet." *J. Pediatr.* 104(3):473-476. doi: 10.1016/S0022-3476(84)81120-8.

Rhomberg, LR; Lewandowski, TA. 2006. "Methods for identifying a default cross-species scaling factor." *Hum. Ecol. Risk Assess.* 12:1094-1127.

Sakuma, T; Sugiyama, N; Wada, Y. 1992. "The urinary acylcarnitine profile in three cases of transient hyperammonemia of the newborn." *Acta Paediatr.* 81(5):436-438. doi: 10.1111/j.1651-2227.1992.tb12264.x.

Schwab, AJ; Tao, L; Yoshimura, T; Simard, A; Barker, F; Pang, KS. 2001. "Hepatic uptake and metabolism of benzoate: A multiple indicator dilution, perfused rat liver study." *Am. J. Physiol. Gastrointest. Liver Physiol.* 280(6):G1124-G1136.

Scientific Committee on Consumer Products (SCCP). 2005. "Opinion on Benzoic Acid and Sodium Benzoate." SCCP/0891/05. European Commission, Health & Consumer Protection Directorate-General. 30p., June 21. Accessed at http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_015.pdf.

Sharp, RA; Lang, CC. 1987. "Hyperammonaemic encephalopathy in chronic myelomonocytic leukaemia (Letter)." *Lancet* 329(8536):805. doi: 10.1016/S0140-6736(87)92827-3.

Shen, DD. 2013. "Toxicokinetics." In *Casarett and Doull's Toxicology: The Basic Science of Poisons (Eighth Edition).* (Ed: Klaassen, CD), McGraw-Hill Education, New York, NY. p367-390.

Simell, O; Sipila, I; Rajantie, J; Valle, DL; Brusilow, SW. 1986. "Waste nitrogen excretion via amino acid acylation: Benzoate and phenylacetate in lysinuric protein intolerance." *Pediatr. Res.* 20(11):1117-1121. doi: 10.1203/00006450-198611000-00011.

Simkin, JL; White, K. 1957. "The formation of hippuric acid; The influence of benzoate administration on tissue glycine levels." *Biochem. J.* 65(3):574-582.

Sushma, S; Dasarathy, S; Tandon, RK; Jain, S; Gupta, S; Bhist, MS. 1992. "Sodium benzoate in the treatment of acute hepatic encephalopathy: A double-blind randomized trial." *Hepatology* 16(1):138-144. doi: 10.1002/hep.1840160123.

Takeda, E; Kuroda, Y; Toshima, K; Watanabe, T; Naito, E; Miyao, M. 1983. "Effect of long-term administration of sodium benzoate to a patient with partial ornithine carbamoyl transferase deficiency." *Clin. Pediatr. (Phila)* 22(3):206-208.

Thabrew, MI; Bababunmi, EA; French, MR. 1980. "The metabolic fate of [14C] benzoic acid in protein-energy deficient rats." *Toxicol. Lett.* 5(6):363-367. doi: 10.1016/0378-4274(80)90016-8.

Tremblay, GC; Qureshi, IA. 1993. "The biochemistry and toxicology of benzoic acid metabolism and its relationship to the elimination of waste nitrogen." *Pharmacol. Ther.* 60(1):63-90. doi: 10.1016/0163-7258(93)90022-6.

Trijbels, JM; Monnens, LA; van der Zee, SP; Vrenken, JA; Sengers, RC; Schretlen, ED. 1974. "A patient with nonketotic hyperglycinemia: Biochemical findings and therapeutic approaches." *Pediatr. Res.* 8(5):598-605. doi: 10.1203/00006450-197405000-00009.

Tuchman, M; Mauer, SM; Holzknecht, RA; Summar, M; Vnencak-Jones, CL. 1992. "Prospective versus clinical diagnosis and therapy of acute neonatal hyperammonaemia in two sisters with carbamyl phosphate synthetase deficiency." *J. Inherit. Metab. Dis.* 15(2):269-277. doi: 10.1007/BF01799641.

Uribe, M; Bosques, F; Marin, E; Cervera, E; Gil S; Luis Poo, J; Garcia Compean, D; Santoyo, R; Huerta, E; Garcia-Ramos, G; Cadena, M; Merikansky, A; Robledo, J; Cortes, M; Guevara, A; Lopez, N; Aguilar, A; Alejandra Ochoa, E. 1990. "Sodium benzoate in portal-systemic-encephalopathy-induced blood ammonia normalization and clinical improvement. Interim report of a double-blind multicenter trial." *Rev. Invest. Clin.* 42(Suppl.):149-154.

US EPA. 2002. "A Review of the Reference Dose and Reference Concentration Processes (Final)." Risk Assessment Forum, Reference Dose/Reference Concentration (RfD/RfC) Technical Panel. EPA/630-P-02/002F. 192p., December.

US EPA. 2004. "An examination of EPA risk assessment principles and practices." Office of the Science Advisor, Risk Assessment Task Force. 192p., March.

US EPA. 2011a. "Recommended Use of Body Weight(3/4) as the Default Method in Derivation of the Oral Reference Dose (Final)." Risk Assessment Forum. EPA/100/R11/0001. 50p.

US EPA. 2011b. "Highlights of the Exposure Factors Handbook." Office of Research and Development. US EPA, National Center for Environmental Assessment (NCEA). EPA/600/R-10/030. 72p., October.

US Food and Drug Administration (US FDA). 1973a. "Select Committee on GRAS Substances (SCOGS) Opinion: Benzoic Acid (CAS No. 65-85-0)." Accessed at http://www.fda.gov/Food/IngredientsPackaging Labeling/GRAS/SCOGS/ucm260036.htm.

US Food and Drug Administration (US FDA). 1973b. "Select Committee on GRAS Substances (SCOGS) Opinion: Sodium Benzoate (CAS No. 532-32-1)." Accessed at http://www.fda.gov/Food/Ingredients PackagingLabeling/GRAS/SCOGS/ucm260074.htm.

US Food and Drug Administration (US FDA). 2004a. "Clinical Pharmacology and Biopharmaceutics Review(s) for Ammonul." Center for Drug Evaluation and Research. 16p.

US Food and Drug Administration (US FDA). 2004b. "Pharmacology/Toxicology Review and Evaluation for Ammonul." Center for Drug Evaluation and Research. 16p.. December 8. Accessed at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/020645s000_PharmR.pdf.

US Food and Drug Administration (US FDA). 2005. "Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers." Center for Drug Evaluation and research (CDER). 30p., July.

US Food and Drug Administration (US FDA). 2016. "Listing of specific substances affirmed as GRAS: Benzoic acid." 21 CFR 184.1021. Accessed at https://www.gpo.gov/fdsys/pkg/CFR-2016-title21-vol3/pdf/CFR-2016-title21-vol3-sec184-1021.pdf.

Van de Bor, M; Mooy, P; van Zoeren, D; Berger, R; van Gelderen, HH; Teijema, HL. 1984. "Successful treatment of severe carbamyl phosphate synthetase I deficiency." *Arch. Dis. Child*. 59(12):1183-1185.

Walter, JH; Allen, JT; Holton, JB. 1992. "Arginosuccinate synthetase deficiency: Good outcome despite severe neonatal hyperammonaemia." *J. Inherit. Metab. Dis.* 15(2):282-283. doi: 10.1007/BF01799645.

Watson, AJ; Chambers, T; Karp, JE; Risch, VR; Walker, WG; Brusilow, SW. 1985. "Transient idiopathic hyperammonaemia in adults." *Lancet* 326(8467):1271-1274. doi: 10.1016/S0140-6736(85)91554-5.