



Refined Exposure Assessment for 4-MEI for the U.S. Population Based on Quantitative Data from Foods Containing Caramel Color



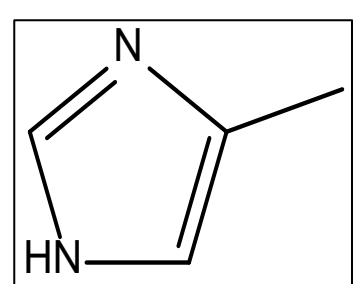
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Background

Concerns have been raised regarding the health effects of 4-methylimidazole (4-MEI), a contaminant found in caramel colors produced using ammonium compounds (Class III and IV caramels). These concerns stem from: 1) results of toxicological testing conducted by the National Toxicology Program (NTP) on 4-MEI in rats and mice, and 2) the levels of 4-MEI that have been found primarily in beverages containing caramel color.

Caramel color is a widely used color additive in food. It is a dark brown liquid or solid produced by controlled heat treatment of food-grade carbohydrates (e.g., sugar), either alone or in the presence of food-grade acid, alkali, and/or salts. There are four classes of caramel color depending on whether the substance is manufactured with or without sulfite and/or ammonia compounds:

- Plain caramel (Class I)
- Sulfite caramel (Class II)
- Ammonia caramel (Class III)
- Sulfite ammonia caramel (Class IV)



Structure of 4-MEI

The current U.S. color additive regulation (21 CFR 73.85) includes all four classes of caramel color, but does not require the product label to differentiate the class of caramel color. Caramel may also be used as a flavoring, the use of which is generally recognized as safe (GRAS) under 21 CFR 182.1235. The use of caramel colors in foods depends on the specific properties of the caramel color (colloidal charge, color intensity) and the desired technical application in the different food matrices. Class III and IV caramels account for approximately 90% of all caramel used in food. Class III caramel is used to color a variety of foods including beer, sauces, confectionary; Class IV caramel is primarily used to color carbonated beverages.

In 2011, the Food and Drug Administration (FDA) received a citizen petition requesting that FDA ban the use of caramel colors produced with ammonia compounds (Class III and IV caramels) due to the presence of 4-MEI. 4-MEI is a chemical impurity that may form at low levels in the manufacture of Class III and IV caramels from a Maillard reaction involving sugar and ammonia. The petition was filed based, in part, on toxicological testing conducted by NTP indicating that there may be carcinogenic concerns with 4-MEI. In 2011, the state of California listed 4-MEI as a Proposition 65 carcinogen. In 2011 and then again in 2012, the European Food Safety Agency (EFSA) indicated that they did not have concerns regarding the exposure to 4-MEI from the use of caramel color in food because combined exposure estimates for the four types of caramel color did not exceed the group acceptable daily intake (ADI) for any population group. In 2014, FDA received another citizen petition asking FDA to set a specification level for 4-MEI in caramel colors, require labeling of the type of caramel on the ingredient list (i.e., identify as Caramel I-IV), and to bar products from claiming "natural" if they contain caramel colors.

In order to respond to the citizen petitions, FDA has conducted a refined exposure assessment based on analytical data of 4-MEI in foods that contain caramel color. This study summarizes the results of this exposure assessment.

Exposure Assessment

Overview

Product labels do not distinguish between the classes of caramel. Therefore, to be conservative, we presumed that all products listing caramel color on the label could be formulated with Class III and IV caramels, which could contribute to 4-MEI exposure. Previously, FDA conducted an exposure estimate using caramel color use levels obtained from industry and EFSA, presuming that all products identified as containing caramel color contained 4-MEI at the specification limit listed in the Food Chemicals Codex for caramel (FCC; 250 mg/kg 4-MEI). In the current exposure estimate, food products containing caramel color were identified, and select products were analyzed for the presence of 4-MEI. The analyzed 4-MEI levels were then used to estimate exposure to 4-MEI in products that were identified as containing caramel color. As the primary focus of the current study was to estimate levels of 4-MEI in products that contained caramel color, foods containing 4-MEI resulting from other sources (e.g., brewed coffee) were not included in the exposure estimate.

Compilation and Sources of Caramel Color in Foods:

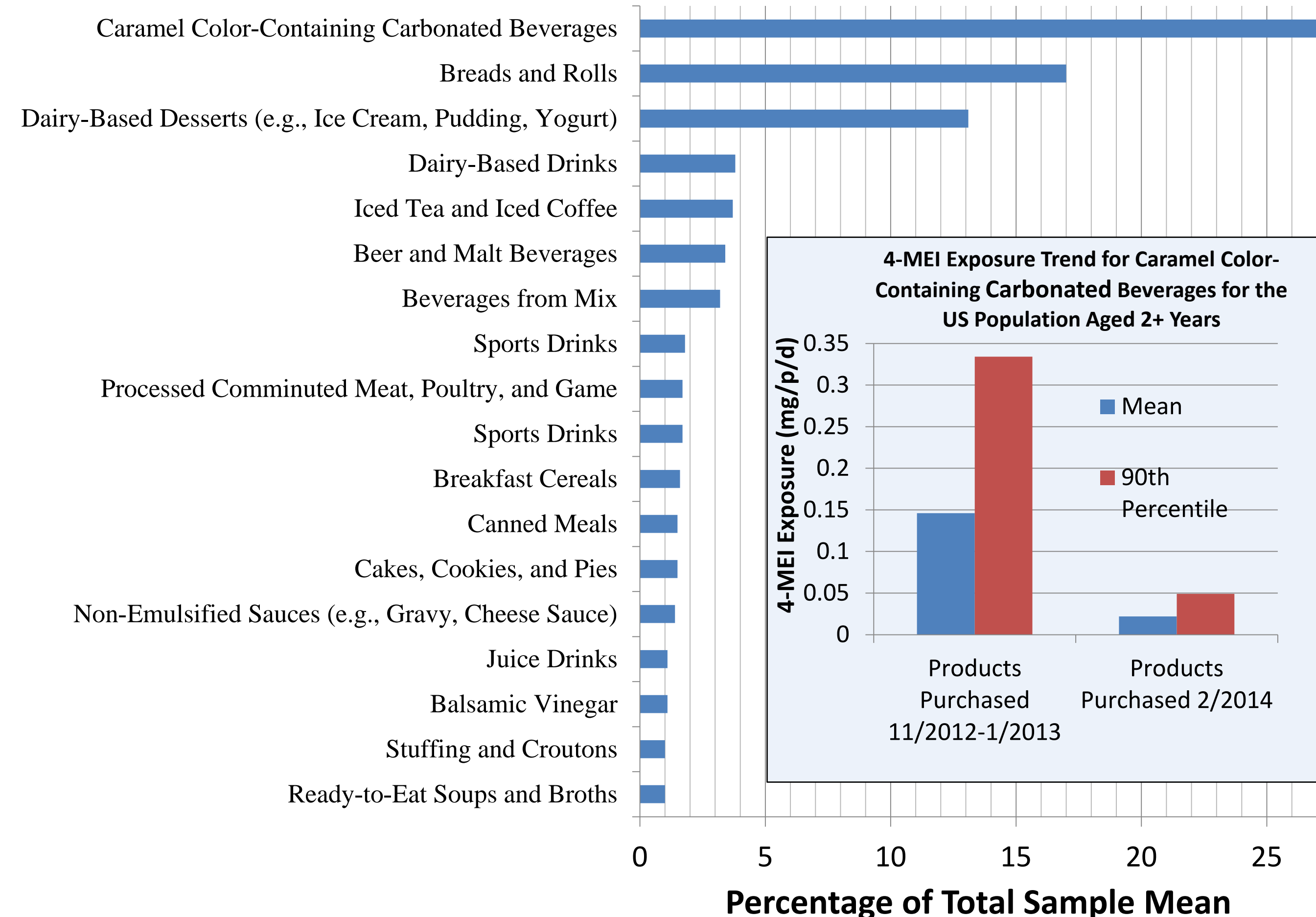
Two different sources were used to identify foods that contained caramel color:

- FoodEssentials LabelBase: A product label database providing access to greater than 250,000 labels containing information from the Gladson and Mintel databases. This database was used to first determine the types of foods that contain caramel color.
 - Gladson Nutrition Database contains over 90% of products in most major consumer packaged goods categories. It includes information such as product images, ingredient information, nutrition information, and universal product codes (UPC).
 - Mintel Global New Products Database (GNPD) monitors product innovation and retail success in the consumer packaged goods market. It contains data similar to that in the Gladson Database for 49 countries in 32 food categories from 1996 to the present.
- Product Label Survey: Data collected from the FoodEssentials LabelBase were verified by conducting a survey of product labels at local grocery stores in the greater Washington D.C. area from April 2012 to July 2014. Product food categories known to currently or previously contain caramel colors were targeted. In addition, when available, information on the use of caramel colors from the websites of food manufacturers and other publicly available websites were used to verify the presence of caramel color in various food products.

Source of 4-MEI Levels in Foods:

• Analytical Data: Based on the label survey, approximately 400 representative products were analyzed for the presence of 4-MEI by a contract laboratory using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The method had a limit of detection of 0.001 mg/kg for beverages and 0.01 mg/kg for other foods. Prior to analysis, all products were prepared as they would be consumed. Results of the level of 4-MEI in each food were provided in µg/ml or µg/g.

Food Categories Contributing 1% or More to the Cumulative Dietary Exposure to 4-MEI for the US Population Aged 2 Years or More



Results

Table 1. Range of 4-MEI Levels Found in Food Labeled as Containing Caramel Color by Broad Food Category

Broad Food Group	Refined Food Group	Range of 4-MEI Levels	
Bread Products	Crackers	0.17-1.21 mg/kg	
	Croutons	3.69 mg/kg	
	Pumpernickel Bread	5.87 mg/kg	
	Rye Bread	1.11 mg/kg	
	Stuffing	0.32 mg/kg	
	Whole Wheat Bread	ND*-1.25 mg/kg	
	Whole Wheat Tortilla	0.44 mg/kg	
Cakes, Cookies and Crackers	Cakes	ND	
	Cereal Bars	0.1 mg/kg	
	Cookies	0.02-0.34 mg/kg	
	Danishes and Pastries	ND	
	Packaged Donuts and Muffins	ND- 0.05 mg/kg	
	Snack Cakes	ND - 0.91 mg/kg	
	Sugar Cones for Ice Cream	0.11-0.16 mg/kg	
	Toaster Pastries	0.07-0.09 mg/kg	
	Candy	Chocolate-Based	ND-0.02 mg/kg
		Hard Candy	ND-0.06 mg/kg
Soft Candy		ND-0.14 mg/kg	
Canned Baked Beans	Canned Baked Beans	0.03-0.08 mg/kg	
	Cola-Type	0.005-0.595 mg/L	
	Ginger Ale	0.003-0.02 mg/L	
Caramel Containing Carbonated Beverages (Purchased November 2012-January 2013)	Pepper-Type	0.02-0.042 mg/L	
	Root Beer	0.06-0.29 mg/L	
	Cola-Type	0.014-0.144 mg/L	
Caramel Containing Carbonated Beverages (Purchased February 2014)	Root Beer	0.018-0.085 mg/L	
	Barbecue Sauce	0.06-0.62 mg/kg	
	Dressing	ND-0.47 mg/kg	
Condiments, Dressings, Gravies and Sauces	Gravies	0.1-0.33 mg/kg	
	Oyster Sauce	0.58 mg/kg	
	Seafood Sauce	0.26 mg/kg	
	Soy Sauce	1.28-1.65 mg/kg	
	Ice Cream	0.01-0.38 mg/kg	
	Pudding	ND-3.1 mg/kg	
	Yogurt	0.6 mg/kg	
	Dessert Sauces and Toppings	Dessert Sauces and Toppings	ND-1.78 mg/kg
		Flavored Powdered Coffee	0.031mg/L
	Grilled or Breaded Fish	Grilled or Breaded Fish	ND-0.03 mg/kg
Cold Cereal		0.01-0.81 mg/kg	
Hot and Cold Cereal	Hot Cereal	ND-0.17 mg/kg	
	Meatless Products	0.19-0.69 mg/kg	

Table 1. Range of 4-MEI Levels Found in Food Labeled as Containing Caramel Color by Broad Food Category (Continued)

Broad Food Group	Refined Food Group	Range of 4-MEI Levels
Other Beverages	Alcoholic Spirits**	ND-0.047 mg/L
	Beer**	ND-0.042 mg/L
	Juice Drinks	0.003 mg/L
	Iced Tea	0.005-0.055 mg/L
	Prepared Powdered Dairy-Based Beverage	0.11 mg/L
	Sports Drinks	ND-0.02 mg/L
	Pancake Syrup	0.14-0.24 mg/kg
Prepared Meals (Includes Canned, Frozen, and Packaged)	Prepared Meals (Includes Canned, Frozen, and Packaged)	ND-0.662 mg/kg
	Processed Flavored Meats	ND-0.19 mg/kg
Savory Snacks	Savory Snacks	ND-0.26 mg/kg
	Soups	ND-0.36 mg/kg
Toddler Foods	Toddler Foods	0.01-0.13 mg/kg
	Vinegar (Balsamic)	Balsamic Vinegar

*ND = Not Detected at limit of detection

**These products do not have an ingredient label.

Table 2. Cumulative Exposure to 4-MEI Based on Analytical Data and 2007-2010 NHANES 2 Day Dietary Intake Survey

Population Group	Eaters	Low Exposure Scenario (mg/p/d)		Average Exposure Scenario (mg/p/d)		High Exposure Scenario (mg/p/d)	
		Mean	90 th Percentile	Mean	90 th Percentile	Mean	90 th Percentile
Infants aged 0 to 1 year	41	0.02	0.05	0.02	0.05	0.02	0.06
Children aged 1 year	98	0.03	0.08	0.04	0.08	0.04	0.09
Children aged 2-5 years	99	0.04	0.10	0.05	0.10	0.05	0.11
Children aged 6-12 years	100	0.05	0.10	0.06	0.11	0.06	0.13
Teenage boys aged 12-18 years	100	0.06	0.13	0.07	0.15	0.09	0.18
U.S. population aged 2 years or more	100	0.06	0.12	0.07	0.14	0.09	0.19

Table 3. Cumulative Exposure to 4-MEI Based on Analytical Data and 2007-2008 NPD NET-NID 10-14 Day Intake Survey

Population Group	Eaters	Low Exposure Scenario (mg/p/d)		Average Exposure Scenario (mg/p/d)		High Exposure Scenario (mg/p/d)	
		Mean	90 th Percentile	Mean	90 th Percentile	Mean	90 th Percentile
Children aged 1 year	87	0.03	0.07	0.03	0.07	0.03	0.07
Children aged 2-5 years	100	0.04	0.08	0.05	0.08	0.05	0.09
Children aged 6-12 years	100	0.05	0.09	0.05	0.09	0.06	0.10
Teenage boys aged 12-18 years	100	0.06	0.10	0.07	0.12	0.08	0.13
U.S. population aged 2 years or more	100	0.06	0.11	0.07	0.12	0.08	0.14

Conclusions and Future Work

Conclusions and Future Work

- Exposure to 4-MEI was estimated for multiple population groups using both 2 day and 10-14 day dietary intake data. As expected, due to the longer number of survey days, 4-MEI exposure calculated using the NPD NET-NID 10-14 day dietary intake data resulted in an overall lower cumulative exposure across all population groups.
- While industry has undertaken efforts to lower 4-MEI levels in caramel-colored carbonated beverages, these products still represent a significant portion of the cumulative 4-MEI exposure.
- Additional products will be analyzed for 4-MEI in order to enhance the exposure estimate, particularly where limited data were available. For certain product categories, trends in the levels of 4-MEI will be monitored.
- Dietary sources of 4-MEI, other than Class III and IV caramels, will be further investigated. Foods in which 4-MEI could be formed through Maillard reactions will be selected.
- Caramel color samples will be acquired and analyzed for 4-MEI.
- FDA will use the 4-MEI exposure estimates in conjunction with review of the available toxicological data for 4-MEI in order to address the citizen petitions before the Agency.

Exposure Assessment (Continued)

Source of 4-MEI Levels in Foods: (Continued)

- The majority of food samples were analyzed by a contract laboratory, however, some samples were also analyzed by FDA scientists using a similar LC-MS/MS method. Due to the large number of foods containing caramel color, a thorough sampling of all foods identified to contain caramel color was not feasible. Certain types of foods (e.g., colas) were more thoroughly sampled (multiple samples of multiple brands, locations and packaging type) as they were expected to be significant contributors to exposure to 4-MEI. For other food categories, representative foods were chosen and analyzed.

Methods for Estimating Exposure to 4-MEI from Foods Containing Caramel Color

Dietary exposure estimates for 4-MEI from foods containing caramel color were performed using two different sets of food consumption data and for up to six population groups:

Population Groups Included in Exposure Estimate	
2007-2010 NHANES two day dietary intake survey	2007-2008 NPD NET-NID 10-14 day data set using the FARE-NET program
Infants aged 0 to 1 year	Children aged 1 year
Children aged 1 year	Children aged 2-5 years
Children aged 2-5 years	Children aged 6-12 years
Children aged 6-12 years	Teenage boys aged 12-18 years
Teenage boys aged 12-18 years	U.S. population aged 2 years or more

The NPD NET-NID data consist of 10-14 day food diaries for over 5,000 respondents. The FARE-NET program provides consumption data based on data combined from NPD NET-NID and NHANES. The food codes used by the NPD NET-NID data set were mapped to the corresponding NHANES food codes to obtain the mean amount consumed for a given food. The NPD NET-NID does not contain information on persons under the age of 1 year, thus exposure was estimated for only five population groups.

Methods for Estimating Exposure to 4-MEI from Foods Containing Caramel Color (Continued)

All dietary exposures were estimated on an "eaters-only" basis, meaning that the estimate represents the dietary exposure to 4-MEI from individuals in the population who consumed one or more foods that contained 4-MEI over the course of the survey. Dietary exposures were estimated at the mean and the 90th percentile, where the 90th percentile represents those individuals who are the "high intake" consumers of a given food.

The exposure estimate was performed as follows:

- Foods containing caramel color were identified based on label information. These foods were then grouped into 72 food categories. Over 1100 food codes from the NHANES survey were assigned across these food categories.
- For each NHANES food code identified as containing caramel color, a 4-MEI level based on the results of the analytical data was assigned to that food code.
 - An effort was made to directly match 4-MEI levels from the analytical data with as many food codes as possible. However, when a direct match was not possible, a reasonable surrogate was chosen from the available data to estimate the level of 4-MEI.
 - For complex foods (e.g., prepared meals) that were not analyzed, the food was broken down into its constituent parts using recipes from the EPA's Food Commodity Intake Database (FCID). 4-MEI levels were then estimated for each component and summed to yield a final 4-MEI level for the complex food.
- For the estimate using NPD NET-NID data, the NHANES food codes were mapped to NPD NET-NID food codes.
- Three different exposure scenarios were performed for both dietary surveys:
 - Low Exposure Scenario: The lowest 4-MEI analytical value was assigned to each food code.
 - Average Exposure Scenario: The analytical results from multiple samples were averaged for a given food code. When appropriate, market share data were used to generate a weighted average based on 4-MEI levels from multiple brands.
 - High Exposure Scenario: The highest 4-MEI analytical value was assigned to each food code.
 - In cases where data from only one product were represented by a given food code, the same 4-MEI level was used across the low, average and high exposure scenarios.
- For each exposure scenario and each population group, estimates were performed for each individual food category as well as a cumulative exposure that encompassed all 72 food categories.