Assessment of Potential Human Health Risks Posed by Benzene in Beverages

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ABSTRACT: A recent study by the U.S. Food and Drug Administration (FDA) indicated that some beverages contained benzene at levels above the federal drinking water standard of 5 parts per billion (ppb). In tests conducted by the FDA, Crystal Light Sunrise Classic Orange (CLSCO) was reported to contain benzene levels as high as 87.9 ppb. The purpose of the present study was to better characterize benzene concentrations in CLSCO and to quantify potential human health risks. Twenty-eight samples of CLSCO were obtained from retail stores in Houston, Tex., U.S.A. The mean benzene concentrations in 16 oz original and new formulation bottles were 90 and 0.18 ppb, respectively, while 64-oz bottles contained an average of 3.38 ppb. A variety of exposure scenarios were evaluated to determine potential health risks using both deterministic and probabilistic techniques. In the deterministic analyses, upper bound point estimate cancer risks ranged from 5.4E-6 to 8.7E-8, while hazard indices (HI) ranged from 0.28 to 0.00104. Probabilistic analyses were conducted to develop more realistic cancer risk estimates. In these analyses, the 50th and 95th percentile cancer risk estimates were 3.7E-6 and 8.0E-6, and the 50th and 95th percentile hazard indices were 0.19 and 0.42, respectively. In conclusion, all cancer risk estimates and noncancer hazards met the typical health risk benchmarks established by the U.S. regulatory agencies (1E-4 to 1E-6 for cancer and hazard indices less than 1.0).

Keywords: benzene, beverages, food risks, health risk, soft drinks

Introduction

In 1990, the U.S. Food and Drug Administration (FDA) learned that benzene was present in some beverages. It was subsequently determined that benzene could form in beverages containing sodium or potassium benzoate salts and ascorbic acid (vitamin C) or erythorbic acid (vitamin C's isomer) (McNeal and others 1993; Nyman 2006). Formation was found to occur as a result of the decarboxylation of benzoate by a hydroxyl radical, and this reaction could be accelerated by heat and ultraviolet light (Gardner and Lawrence 1993; Nyman 2006). Additionally, investigators noted that the food additive ethylene diamine tetra-acetic acid (EDTA) and nutritive sweeteners such as sugar and high-fructose corn syrup could inhibit or reduce the formation of benzene (Nyman 2006; USFDA 2006a). The benzoate salts are preservatives that are added to beverages to inhibit growth of bacteria, yeasts, and mold, but may also occur naturally in some fruit juices. Vitamin C may be added as a preservative or as a vitamin supplement or may be naturally present in some fruit juices as well (Nyman 2006; USFDA 2006b). As a result of these findings, many manufacturers reformulated their products to reduce or eliminate the formation of benzene.

Nonetheless, in November 2005, the FDA received private laboratory results indicating that benzene was still present at low levels in some beverages containing benzoate salts and ascorbic acid (USFDA 2006b). As a follow-up, FDA's Center for Food Safety and Applied Nutrition (CFSAN) initiated a survey of beverages, with a focus on those beverages that contained both benzoate salts and ascorbic acid or erythorbic acid. As a part of this investigation, CFSAN collected over 100 samples of soft drinks and other beverages from retail stores in Maryland, Virginia, and Michigan. In May 2006, CFSAN released results of its study. Most products were found to contain only low levels of benzene. In fact, only 4 beverage products with added benzoate salts and ascorbic acid were found to contain levels of benzene above the federal maximum contaminant level (MCL) of 5 ppb established by the U.S. Environmental Protection Agency (EPA) for drinking water. These products included Safeway Select Diet Orange Soda, Crush Pineapple, AquaCal Strawberry Flavored Water Beverage, and Crystal Light Sunrise Classic Orange (CLSCO) (USFDA 2006a). Benzene was also detected at levels above 5 ppb in Giant Light Cranberry Juice Cocktail, a product that contains added ascorbic acid but no added benzoates. In this case, the benzene is thought to form as a result of the natural benzoates present in cranberries. In the case of CLSCO, 5 lots were tested. The tested samples of this beverage included the original formulation (which contained sodium benzoate and ascorbic acid) and a reformulated product (hereafter referred to as the "new formulation"). Two lots contained benzene at levels over 70 ppb, though the new formulation was reported to contain < 1 ppb. Because of public concern about potential exposures to benzene in soft drinks and other beverages and because real-world exposures are likely to vary considerably relative to the single specific exposure scenario used to develop the MCL, we concluded that it might be helpful to conduct a follow-up study to better characterize levels of benzene in these products and to characterize the potential human health risks for a number of different possible exposure scenarios using both deterministic and probabilistic risk assessment techniques. For purposes of this follow-up study, we focused on 1 particular product found to contain the highest levels of benzene in the FDA testing—CLSCO. Other potential sources of exposure to benzene were not considered in this analysis.

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Materials and Methods

Sampling design

Data from the FDA testing (USFDA 2006a) were reviewed to identify the specific beverage product to be evaluated in the current study. CLSCO was selected because it was reported to contain some of the highest levels of benzene in the FDA tests and, therefore, would represent a potential worst-case scenario based on data currently available. Because FDA testing had indicated that the reformulated CLSCO product had lower levels of benzene, the goal of the current study was to collect both original and new formulation CLSCO where possible. Information obtained from the Kraft Foods Consumer Relations Dept. indicated that the new and old formulation products could be identified by their packaging, and that a gap in expiration dates existed between the original and new formulation products. These criteria were used in this study to identify original and new formulation CLSCO products.

A list of grocery stores believed to carry the CLSCO product was compiled for the Houston, Tex. area. The list consisted of several local chains, including Randall's, Wal-Mart®, and Kroger stores. The geographic location of each store was determined using a Key Map® of Harris County. Harris County was determined to lie within 149 grids on the Key Map. Each grid of the Key Map was 3 miles (east–west) by 4.5 miles (north–south), and comprised 8640 acres. There were 24 Key Map grids identified that contained at least one of these grocery stores.

Each grocery store was assigned an ID number based on the grid in which it was located, and 3 stores were randomly selected from each grid using a random number generator. Three stores were selected to account for the possibility that every store might not carry the product. If the 1st store that was selected in a grid did not carry the product, then the 2nd and possibly 3rd stores were successively visited until a sample was obtained. The goal was to obtain 1 sample per grid. In accordance to this sampling protocol, samples were acquired from 26 stores in 24 Key Map grids across the Houston area.

Samples were collected on 5 d between June 2, 2006 and June 8, 2006. During the sample collection, it was determined that the CLSCO product was available in 2 sizes: 16- and 64-oz bottles. The significance of this finding was that the 64-oz product did not contain sodium benzoate, a precursor for benzene formation, while the 16-oz product did contain sodium benzoate. Twenty-three sets of 16-oz bottles were collected from stores across the Houston area: 18 were purchased at Randall's stores and 5 were purchased at Wal-Mart stores. In addition, five 64-oz bottles were also collected for comparison purposes as sodium benzoate was not listed as an ingredient for this product. The 64-oz bottles could be found only at Kroger's. Once collected, samples were maintained in air-conditioned environments at all times and were protected from UV light to ensure an accurate representation of the benzene levels in products as they existed on the store shelves.

Chemical analysis

Bottled samples of CLSCO were submitted to Southern Petroleum Laboratories (SPL) in Houston, Tex., U.S.A. for analysis of benzene content using USEPA Method 8260B, a purge-and-trap gas chromatography/mass spectrophotometry (GC/MS) method. Method 8260B is a solid waste method used to analyze volatile organic compounds and is applicable to nearly all types of samples, regardless of water content (USEPA 1996). In accordance with this method, the analytes are introduced directly to a wide-bore capillary column or cryofocused on a capillary precolumn before being flash evaporated to a narrow-bore capillary column for analysis. The column is temperature-programmed to separate the analytes, which are then detected with a mass spectrometer (MS) interfaced to the gas chromatograph (GC).

Sample results (in μg/L) were reported as detected concentrations, as estimated concentrations (J-Flagged; below the practical quantitation limit [PQL] and above the method detection limit [MDL]), and as not detected (U-Flagged; at or above the MDL). The PQL is defined lowest point on the calibration curve used to quantify benzene concentration. The MDL is determined as set forth in 40 CFR Part 136, three times the standard deviation of replicate spiked analysis. The MDL is designed to represent 99% confidence that the analyte concentration is greater than zero. Values for the PQL and MDL were provided by the laboratory.

Data analysis

The concentration data characterized in this analysis reflected the 3 types of CLSCO products sampled: 16-oz original formulation samples, 16-oz new formulation samples, and 64-oz samples. Each product type was characterized by its mean, median, and range. Ninety-five percent (95%) upper confidence limits (UCL) on mean concentrations were calculated using ProUCL. U-Flagged data were assigned the full value of the MDL in 95% UCL calculations. J-flagged data, reported as estimated concentrations, were used as reported in 95% UCL calculations. Data characterization for each of the 3 product types is presented in Table 1, along with the distributions and parameter estimates used by ProUCL to calculate 95% upper confidence limits on the mean. All benzene concentrations are presented in micrograms per liter unless otherwise noted.

Exposure scenarios

It was assumed that individuals purchased either 16- or 64-oz bottles of CLSCO. Accordingly, 2 primary exposure scenarios were developed, each with different exposure concentration models. Since there was no evidence to indicate that the benzene concentration in the 64-oz bottles changed over time, the benzene concentration for individuals consuming the 64-oz bottles was based on a single value in the deterministic analyses (that is, point estimates of risk and hazard) or a single distribution for the probabilistic analyses. Since the formulation of CLSCO in 16-oz bottles changed after 6 y, exposure to CLSCO in 16-oz bottles was assessed based on benzene concentrations in each of the 2 product types: one to characterize the original formulation and the other to characterize the new formulation.

Thirteen exposure scenarios were developed to assess benzene intake associated with consumption of CLSCO in 16-oz bottles. These scenarios are depicted in Table 2. For purposes of this analysis, it was assumed teens and adults were the primary consumers of CLSCO, because representatives from Kraft Foods indicated that this product is not marketed to young children. Based on the identification of these 2 primary consumer groups, it was assumed that exposure began at age 12. It was also assumed, based on information obtained from the Kraft Foods Consumer Relations Dept, that the original formulation of CLSCO was first sold in 2000 and continued to be sold until 2006, when the new formulation was introduced. Exposure scenarios 1 through 7 were designed to characterize individuals consuming the original formulation of CLSCO for 1 to 6 y beginning at age 12. Exposure scenarios 8 through 13 depict individuals of different age beginning with 6 y of exposure to original formulation in 2000. The final exposure scenario evaluated represents an individual who consumed the 64-oz CLSCO product throughout his/her teen and adult years.

Ingestion parameters: ingestion rate and frequency. The EPA Exposure Factors Handbook (USEPA 1997) was reviewed to identify

potential ingestion rates for CLSCO, a beverage that is classified as a fruit flavored drink. Of the categories of beverages provided in the Exposure Factors Handbook, it was determined that the category most representative of CLSCO was "fruit drinks." The mean intake of "fruit drinks" for consumers specified in the EPA Exposure Factors Handbook was determined to be 0.123 L/d (that is, 4.2 oz/d). However, because the goal was to develop a high-end or worst-case exposure estimate in the deterministic analyses, the ingestion rate for CLSCO was assumed to be one 16-oz (473 mL) bottle per day. This is believed to represent a reasonable worst-case assumption because it seemed unlikely that an individual would open a bottle and drink only 4.2 oz. For probabilistic analysis, a triangular distribution ranging from 90% of 1 bottle (430 mL) to 2 bottles (946 mL), with the most likely value equal to 1 bottle (473 mL), was used. For frequency of ingestion, 365 d per year (7 d per week) was assumed for point estimates. For probabilistic analysis, a uniform distribution ranging from 208 d per year (4 d per week) to 365 d per year was assumed.

Body weight. Age-specific average body weights and normal distribution parameters for teens were obtained from Finley and others (1994). For teens, intake was calculated using both the average value and the age-specific value in a year-by-year calculation. For adults, the point estimate value and normal distribution parameters were obtained from the USEPA Exposure Factors Handbook (USEPA 1997). All body weight parameters are presented in Table 3.

Toxicity parameters. The USEPA has developed 2 cancer slope factors for benzene: an upper-bound slope factor of 1.50×10^{-2} and a lower-bound slope factor of 5.50×10^{-2} (USEPA 1988). Both of these cancer slope factors were derived based on extrapolation from inhalation data obtained from occupational studies. The oral reference dose (RfD) for noncarcinogenic effects is 4×10^{-3} mg/kg/d, and was derived based on decreased lymphocyte counts seen in a cohort of workers occupationally exposed to benzene through inhalation (Rothman and others 1996).

Estimation of risk and hazard

Because there are 2 sets of concentration data for the 16-oz formulation (original and new formulation products), risk calculations were performed in a way that was flexible enough to allow quantification of exposure to each formulation, while allowing cumulative risk and hazard index estimates to be calculated. The general form of the intake equation is illustrated in Eq. 1.

$$\text{Intake} = \frac{Cw * CF * IR * EF * ED}{BW * AT} \tag{1}$$

where Cw is the concentration of benzene in CLSCO (μg/L), CF is a conversion factor equal to 0.001 mg/L per μg/L, IR is ingestion rage (L/d), EF is exposure frequency (d/y), ED is exposure duration (yr), BW is body weight (kg), and AT is averaging time (d). To generalize this equation, several terms were made variable depending upon the exposure scenario. The concentration term was variable according to the 2 formulations of 16-oz CLSCO consumed. The body weight term was variable to accommodate teen and adult exposure groups. The exposure duration term was variable to accommodate different lengths of exposure to original and new formulations. To accommodate these variables, Eq. 1 is generalized to yield Eq. 2:

$$\text{Dose} = \left[\frac{CF * IR * EF}{AT} * \left(\sum_{i-1}^{6y} \frac{Cw * ED}{BW}\right)\right]_{\text{teen}} + \left[\frac{CF * IR * EF}{AT} * \left(\sum_{i-1}^{52y} \frac{Cw * ED}{BW}\right)\right]_{\text{adult}} \tag{2}$$

In Eq. 2, benzene concentration varied with the formulation of CLSCO consumed, body weight varied with age, and exposure duration was equal to 1 y since intake was evaluated on a yearly basis in this analysis. There were a total of 6 y under consideration for exposure during the teen years, from age 12 to 18. There were a total of 52 y under consideration for exposure during the adult years, from age 18 to 70. For the carcinogenic risk calculations, the averaging time in Eq. 2 was assumed to be 70 y for adults and teens. For the hazard index calculations, the averaging time was assumed to be 6 y for teens and 52 y for adults. This equation allows calculations to be done on a year-by-year basis so as to accommodate the different exposure scenarios being evaluated. Risk and hazard were then calculated according to Eq. 3 and 4.

$$\text{Risk} = \text{Intake} * \text{Slope Factor (SF)} \tag{3}$$

Table 1 — Benzene (μg/L) in sampled Crystal Light Sunrise Classic Orange products.

Product type	Number of samples	Number of samples detected/ J-flag / U-flag	Range	Mean	Median	SD	95% UCL	Distribution	Parameters
CLSCO 16 oz, original formulation	5	5 / 0 / 0	23 to 140	90.0	80.0	47.06	135	Normal	Mean = 90, SD = 40.06
CLSCO 16 oz, new formulation	18	0 / 12 / 6	0 to 0.35	0.238	0.220	0.10	0.26	Custom discrete, based on analytical data	Value (*P*) 0.053 (0.33) 0.19 (0.056) 0.20 (0.056) 0.21 (0.056) 0.22 (0.222) 0.23 (0.056) 0.24 (0.056) 0.25 (0.056) 0.30 (0.056) 0.35 (0.056)
CLSCO 64 oz	5	5 / 0 / 0	2.7 to 3.8	3.38	3.50	0.44	3.80	Normal	Mean = 3.38, SD = 0.44

SD = standard deviation.

$$\text{Hazard Index} = \text{Intake/Reference Dose(RfD)} \quad (4)$$

Using these equations, 3 sets of calculations were performed. First a conservative point estimate of risk and hazard was calculated using average body weights for the teens and adults, and 95% upper confidence limits (UCLs) on the mean for benzene concentration in original formulation CLSCO. A 2nd point estimate was calculated by allowing the body weight and exposure concentration to vary from year to year. Body weights varied according to the average body weights reported in Finley and others (1994) during the teen years, while a single value was used for adults. The concentration term varied according to the formulation of CLSCO consumed, year by year. To characterize each formulation, a 95% UCL was used. Third, a Monte Carlo analysis was performed using the approach in which body weight varied with age and exposure concentration varied according to formulation of CLSCO consumed, as determined on a year-by-year basis. In this analysis, distributions were used to characterize body weights and exposure concentrations, along with other parameters such as the ingestion rate and exposure frequency. These terms are described further in the Results and Discussion section.

Table 2—Exposure scenarios.

Scenario	Original formulation	New formulation	64-oz formulation
1	6 y, age 12 to 18	Age 18 to 70	None
2	5 y, age 12 to 17	Age 17 to 70	None
3	4 y, age 12 to 16	Age 16 to 70	None
4	3 y, age 12 to 15	Age 15 to 70	None
5	2 y, age 12 to 14	Age 14 to 70	None
6	1 year, age 12 to 13	Age 13 to 70	None
7	None	Age 12 to 70	None
8	6 y, age 13 to 19	Age 19 to 70	None
9	6 y, age 14 to 20	Age 20 to 70	None
10	6 y, age 15 to 21	Age 21 to 70	None
11	6 y, age 16 to 22	Age 22 to 70	None
12	6 y, age 17 to 23	Age 23 to 70	None
13	6 y, age 18 to 24	Age 24 to 70	None
64 oz	None	None	Age 12 to 70

Risk assessment and Monte Carlo simulations

Risk assessment procedures and assumptions were based on guidance provided by USEPA (USEPA 1989, 1997). Probabilistic analyses were conducted using Decisioneering's Crystal Ball (version 7.3; Denver, Colo., U.S.A.) and Microsoft Excel (Redmond, Wash., U.S.A.). A minimum of 5000 iterations were completed for each simulation. A comprehensive list of exposure parameters used in both deterministic and probabilistic assessments is provided in Table 3.

Results and Discussion

Benzene concentrations in crystal light sunrise classic orange

Sample collection of the 16-oz product in retail stores across the Houston area yielded 5 samples of the original formulation

Table 3—Exposure assumptions used in deterministic and probabilistic analyses.

Parameter	Point estimate	Distribution
Concentration of benzene (original formulation), μg/L	134.87[a]	Normal: mean = 90 SD = 4.7
Concentration of benzene (new formulation), μg/L	0.26[a]	Custom distribution: resampled from concentration data (Table 1)
Concentration of benzene (64-oz formulation), μg/L	3.8[a]	Normal: mean = 3.38 SD = 0.44
Ingestion Rate (IR), L/day	0.473	Triangular: most likely = 0.473 Range = 0.43 to 0.95
Exposure frequency (EF), days	365	Uniform: 208 to 365 d
Exposure duration (ED), year		
Teen	6	
Adult	52	
Body weight (BW), kg		
Teen 12 to 13	44.9	Normal: mean = 44.9 SD = 10
Teen 13 to 14	49.5	Normal: mean = 49.5 SD = 10.5
Teen 14 to 15	56.6	Normal: mean = 56.6 SD = 10.3
Teen 15 to 16	60.5	Normal: mean = 60.5 SD = 9.7
Teen 16 to 17	67.7	Normal: mean = 67.7 SD = 11.6
Teen 17 to 18	67.0	Normal: mean = 67 SD = 11.5
Teen, average	57.7	
Adult	70.0	Normal: mean = 71.9 SD = 15.9
Averaging time (AT)	25550	
Benzene slope factor (upper bound), per (mg/kg)/d	1.50E-2	
Benzene slope factor (lower bound), per (mg/kg)/d	5.50E-2	
Reference dose, mg/kg/d	4.00E-3	

[a]Values represent 95% upper confidence limits on the mean, determined by ProUCL.
SD = standard deviation.

and 18 samples of the new formulation of CLSCO. The mean benzene concentration was 90 ppb in the original formulation and 0.18 ppb in the new formulation, indicating that product reformulation was successful in reducing the levels of benzene in the 16-oz bottles of CLSCO (Table 1). With respect to the new formulation, many of the measurements were below the PQL (0.5 to 1.0 ppb). For the 64-oz bottles, our analysis demonstrated that in the 5 samples obtained, the mean benzene levels were 3.38 ppb. This is noteworthy because sodium benzoate was not listed as an ingredient on the label of the 5 bottles of the 64-oz formulation that were obtained.

Deterministic estimates of risk

Point estimates of cancer risk and the noncancer hazard were calculated using 2 methods. First, a conservative calculation was performed using the 95% UCL of the measured benzene concentrations and average body weights for adults and teens. These results are presented in Table 4. Exposure duration was limited to 6 y in calculating risk and hazard index associated with original formulation CLSCO, because this formulation was available for only 6 y from 2000 to 2006. Using this technique, conservative estimates of lifetime cumulative risk and hazard index associated with consuming the 16-oz bottles were determined to be 5.3E-6 and 0.28, respectively. These estimates were obtained by adding the upper bound teen risk associated with original formulation exposure to the upper bound adult risk associated with new formulation exposure. The upper bound cumulative lifetime risk and hazard index associated with consuming the 64-oz bottles were determined to be 1.2E-6 and 6.4E-3, respectively.

Point estimates of risk and hazard were also estimated by allowing the benzene concentration to change depending on the formulation of CLSCO consumed, and body weight to change based on age. Equation 2 was used for these calculations, and the different exposure scenarios are depicted in Table 2. Risk and hazard were calculated for 13 different exposure scenarios, representing a range of possible exposures. The highest estimates of intake, and accordingly risk and HI, were associated with exposure to original formulation CLSCO during teen years. Exposure scenario 1 generated the highest estimates of cancer risk, ranging from 1.5E-6 to 5.4E-6, and hazard index, 0.28. Risk estimates associated with exposure to 64-oz bottles did not incorporate a changing benzene concentration, but did include age-specific body weights. Risk estimates for the 64-oz formulation were found to range from 3.3E-7 to 1.2E-6, and HI was 0.014. A complete listing of risk and hazard estimates associated with this method is provided in Table 5 and 6, respectively.

Probabilistic estimates of risk

A probabilistic assessment was conducted using Monte Carlo analysis. The point estimate model in which body weight changed with age and benzene concentration varied according to the formulation of CLSCO consumed was modified to incorporate distributions. Risk and HI were calculated for 13 exposure scenarios associated with 16-oz bottles of CLSCO, and 1 exposure scenario associated with drinking 64-oz bottles of CLSCO. The result of the Monte Carlo analysis was a distribution of lifetime risk and HI for each exposure scenario.

Of the 13 exposure scenarios modeled, the highest estimates of risk were generally associated with the number of years exposed to original formulation CLSCO, and with exposure during the teen years when body weight was lower. As shown in Table 7, the maximum risk estimates were generated for exposure scenario 1, and ranged from 1.0E-6 to 3.7E-6 at the 50th percentile of the risk distribution, and 2.2E-6 to 8.0E-6 at the 95th percentile of the risk

Table 4—Point estimates of risk and hazard.

	Teen		Adult	
Formulation	Risk[a]	Hazard index	Risk[a]	Hazard index
16-oz original formulation	1.4E-6 to 5.2E-6	2.8E-1	1.2E-6 to 4.3E-6	2.6E-2
16-oz new formulation	2.9E-9 to 1.1E-8	5.6E-4	2.1E-8 to 7.6E-8	4.7E-4
64-oz formulation	4.0E-8 to 1.5E-7	7.8E-3	2.9E-7 to 1.1E-6	6.4E-3

[a]Risk calculated based on lower bound and upper bound slope factors for benzene.

Table 5—Point estimates[a] of cancer risk by exposure scenario.

	Age (year)														
	Teen (years)						Adult (years)								
scenario	12	13	14	15	16	17	18	19	20	21	22	23	24	70	Total
1	1.1E-06	1.0E-06	8.9E-07	8.3E-07	7.4E-07	7.5E-07	7.6E-08[b]								5.4E-06
2	1.1E-06	1.0E-06	8.9E-07	8.3E-07	7.4E-07	1.5E-09	7.6E-08[b]								4.7E-06
3	1.1E-06	1.0E-06	8.9E-07	8.3E-07	1.5E-09	1.5E-09	7.6E-08[b]								3.9E-06
4	1.1E-06	1.0E-06	8.9E-07	1.7E-09	1.5E-09	1.5E-09	7.6E-08[b]								3.1E-06
5	1.1E-06	1.0E-06	1.8E-09	1.7E-09	1.5E-09	1.5E-09	7.6E-08[b]								2.2E-06
6	1.1E-06	2.1E-09	1.8E-09	1.7E-09	1.5E-09	1.5E-09	7.6E-08[b]								1.2E-06
7	2.3E-09	2.1E-09	1.8E-09	1.7E-09	1.5E-09	1.5E-09	7.6E-08[b]								8.7E-08
8		1.0E-06	8.9E-07	8.3E-07	7.4E-07	7.5E-07	7.2E-07	7.5E-08[b]							5.0E-06
9			8.9E-07	8.3E-07	7.4E-07	7.5E-07	1.4E-06[b]		7.3E-08[b]						4.7E-06
10				8.3E-07	7.4E-07	7.5E-07	2.1E-06[b]			7.2E-08[b]					4.5E-06
11					7.4E-07	7.5E-07	2.9E-06[b]				7.0E-08[b]				4.4E-06
12						7.5E-07	3.6E-06[b]					6.9E-08[b]			4.4E-06
13							4.3E-06[b]						6.7E-08[b]		4.4E-06
64 oz	3.1E-08	2.9E-08	2.5E-08	2.3E-08	2.1E-08	2.1E-08	1.0E-06[b]								1.2E-06

Original Formulation New Formulation 64 oz Formulation No Exposure

[a]Risk estimates calculated using upper bound slope factor.
[b]Values centered across years represents cumulative value over all years.

distribution. For individuals drinking 64-oz bottles of CLSCO risk estimates at the 50th percentile ranged from 2.9E-7 to 1.0E-6 and from 5.2E-7 to 1.9E-6 at the 95th percentile.

The same general trend was observed for the HI estimates; higher calculated HIs were generally associated with the number of years exposed to original formulation CLSCO and with exposure during the teen years when body weight was lower. As shown in Table 7, maximum estimates were observed for exposure scenario 1; 0.19 at the 50th percentile of the HI distribution and 0.42 at the 95th percentile of the HI distribution. For individuals drinking 64-oz bottles of CLSCO, the HI estimate was 0.013 at the 50th percentile and 0.022 at the 95th percentile.

Comparing the distributions of risk and hazard developed for exposure scenarios 1 to 13, as well as the 64-oz exposure scenario, there was a gradual shift to lower risk levels when going from scenarios 1 to 6 and a fairly dramatic shift, including a tightening of the distribution, for exposure scenario 7. In contrast, there was very little difference in the distribution of risk estimates for exposure scenarios 8 to 13. A similar tightening of the risk distribution was observed for the 64-oz exposure scenario. In contrast, for hazard, a gradual decrease in the 25th, 50th, and 75th percentiles was observed when going from exposure scenarios 1 to 7 as well as from exposure scenarios 8 to 13.

A sensitivity analysis was performed on the parameters associated with each exposure scenario. These data are presented in Table 8. Scenarios 1 and 8 through 13 show the changes in sensitivity to parameters as the 6-y period of exposure moves through the teen years and into the adult years. The benzene concentration associated with the original formulation accounts for the greatest contribution to variance across all scenarios, and ranged from 69% to 79%. The contribution to variance was 79% for scenario 1, when the exposure period to original formulation CLSCO was exclusively in the teen years, and gradually decreases to 69% as the period of exposure to the original formulation increases during the adult years. The body weight distribution for the adult also gains importance in sensitivity as the period of exposure to the original formulation increases during the adult years, increasing from near zero contribution to variance in scenario 1 to 13% in scenario 13. For scenarios 1 through 13, ingestion rate and exposure frequency account for approximately 11% and 7.5% contribution to variance, respectively. For the 64-oz drinker, adult body weight, ingestion rate, and exposure frequency show contributions to variance of 32%, 31%, and 23%, respectively.

These trends in sensitivity explain the differences in calculated risk as the exposure period to original formulation CLSCO moves across age groups (from teen to adult). While one would expect to see differences between different exposure scenarios related to body weight, those differences are small because of the relatively small contribution to variance of body weight when compared with the dominant contribution to variance of benzene concentration in the original formulation of CLSCO. For example, risk estimates for exposure scenario 1 ranged from 1.0E-6 to 3.7E-6 at the 50th percentile and 2.2E-6 to 8.0E-6 at the 95th percentile. Risk estimates for exposure scenario 13 ranged from 7.7E-7 to 2.8E-6 at the 50th percentile and from 1.8E-6 to 6.7E-6 at the 95th percentile. Risk estimates for the teen group were approximately 30% higher at the 50th percentile, and approximately 20% higher at the 95th percentile.

It is instructive to compare point estimates of risk with the probabilistic estimates. The 1st point estimate was generated using average body weights for each exposure group and 95% UCLs on the mean for exposure concentration of benzene in CLSCO. The range of risk was 1.4E-6 to 5.2E-6, and the HI was 0.28. In the 2nd point estimate, body weights varied with age of exposure and benzene concentration varied with formulation of CLSCO consumed. These techniques produced a nearly identical result for the maximally impacted receptor (scenario 1): the risk estimate ranged from 1.5E-6 to 5.4E-6 and HI was equal to 0.28. While it is useful to evaluate a range of exposures for certain variables, body weight did not demonstrate sensitivity in risk and hazard estimates for the maximally exposed individual.

Probabilistic risk estimates for the maximally exposed individual (exposure scenario 1) range from 1.0E-6 to 3.7E-6 at the 50th percentile and 2.2E-6 to 8.0E-6 at the 95th percentile. This places the point risk estimates at about 77.5th percentile on the risk distributions (lower or upper bound, as appropriate). The same can be said for HI: the point estimate 0.28 lies at about the 77.5th percentile on the HI distribution. Remembering that the risk and HI calculations are highly dependent on concentration of benzene in the original formulation of CLSCO, it is useful to look at the 95% UCL on the mean that was used for point estimates, 134.87 μg/L. This 95% UCL on the mean lies at about the 82nd percentile on the distribution of benzene concentration for original formulation

Table 6—Point estimates of hazard by exposure scenario.

	Age (year)														
	Teen (years)						Adult (years)								
scenario	12	13	14	15	16	17	18	19	20	21	22	23	24	70	Total
1	5.9E-02	5.4E-02	4.7E-02	4.4E-02	3.9E-02	4.0E-02	4.7E-4[a]								2.8E-01
2	5.9E-02	5.4E-02	4.7E-02	4.4E-02	3.9E-02	8.1E-05	4.7E-4[a]								2.4E-01
3	5.9E-02	5.4E-02	4.7E-02	4.4E-02	8.0E-05	8.1E-05	4.7E-4[a]								2.0E-01
4	5.9E-02	5.4E-02	4.7E-02	9.0E-05	8.0E-05	8.1E-05	4.7E-4[a]								1.6E-01
5	5.9E-02	5.4E-02	9.6E-05	9.0E-05	8.0E-05	8.1E-05	4.7E-4[a]								1.1E-01
6	5.9E-02	1.1E-04	9.6E-05	9.0E-05	8.0E-05	8.1E-05	4.7E-4[a]								6.0E-02
7	1.2E-04	1.1E-04	9.6E-05	9.0E-05	8.0E-05	8.1E-05	4.7E-4[a]								1.0E-03
8		5.4E-02	4.7E-02	4.4E-02	3.9E-02	4.0E-02	4.4E-3	4.6E-4[a]							2.3E-01
9			4.7E-02	4.4E-02	3.9E-02	4.0E-02	8.8E-3[a]		4.5E-4[a]						1.8E-01
10				4.4E-02	3.9E-02	4.0E-02	1.3E-2[a]			4.4E-4[a]					1.4E-01
11					3.9E-02	4.0E-02	1.8E-2[a]				4.3E-4[a]				9.7E-02
12						4.0E-02	2.2E-2[a]					4.2E-4[a]			6.2E-02
13							2.6E-2[a]						4.1E-4[a]		2.7E-02
64 oz	1.7E-03	1.5E-03	1.3E-03	1.2E-03	1.1E-03	1.1E-03	6.4E-03[a]								1.4E-02

Original Formulation New Formulation 64 oz Formulation No Exposure

[a]Values centered across years represents cumulative value over all years.

of CLSCO. The risk values that correspond to the 82nd percentile on the risk distribution range from 1.5E-6 to 5.8E-6, within 10% of the point estimates. This is a direct result of the large contribution to variance of the concentration term. In instances where the concentration term comprises a majority of the variance, the 95th percentile of the risk distribution will overestimate the worst-case point estimate conducted with the 95% UCL on the mean. Further, the percentile on the concentration distribution that corresponds to the 95% UCL on the mean will be a good predictor for the percentile on the risk distribution to which the point estimate of risk corresponds.

Uncertainty

To develop estimates of cancer risk and noncancer hazard, it was necessary to make assumptions regarding consumption of CLSCO. Two key conservative assumptions regarding consumption were made: exposure occurred over a period of 58 total years, 7 d a week (point estimates) or 4 to 7 d per week (probabilistic estimates). These assumptions were made to ensure that the assessment would not underpredict the actual health risks for a wide range of exposure groups. While assumptions regarding consumption were designed to be flexible on a year-by-year basis, certainly consumption patterns outside of our exposure assumptions are possible. Additionally, the age of consumers is also a source of uncertainty. Our exposure scenario assumes that consumption of CLSCO by individuals under the age of 12 is unlikely. While the assessment yielded slightly higher risk and hazard estimates for younger age groups, the estimates were remarkably similar for those individuals assumed to be drinking the same product type (that is, either original or new formulation), due in large part to the lack of sensitivity of the estimates to body weight as demonstrated by low contribution to variance (Table 8).

The risk calculations documented in this article use the CLSCO 16-oz formulations available on the market since the year 2000. It

Table 7—Probabilistic estimates of risk and hazard.

		Percentile of the risk distribution			
Scenario	Risk/hazard index	25%	50%	75%	95%
1	Risk, upper bound slope factor	2.4E-06	3.7E-06	5.2E-06	8.0E-06
	Risk, lower bound slope factor	6.5E-07	1.0E-06	1.4E-06	2.2E-06
	Hazard index	1.2E-01	1.9E-01	2.7E-01	4.2E-01
2	Risk, upper bound slope factor	2.0E-06	3.2E-06	4.5E-06	6.9E-06
	Risk, lower bound slope factor	5.6E-07	8.6E-07	1.2E-06	1.9E-06
	Hazard index	1.1E-01	1.7E-01	2.4E-01	3.6E-01
3	Risk, upper bound slope factor	1.7E-06	2.7E-06	3.8E-06	5.8E-06
	Risk, lower bound slope factor	4.7E-07	7.2E-07	1.0E-06	1.6E-06
	Hazard index	8.9E-02	1.4E-01	2.0E-01	3.1E-01
4	Risk, upper bound slope factor	1.4E-06	2.1E-06	3.0E-06	4.7E-06
	Risk, lower bound slope factor	3.7E-07	5.7E-07	8.2E-07	1.3E-06
	Hazard index	7.0E-02	1.1E-01	1.6E-01	2.5E-01
5	Risk, upper bound slope factor	9.7E-07	1.5E-06	2.1E-06	3.4E-06
	Risk, lower bound slope factor	2.6E-07	4.1E-07	5.8E-07	9.2E-07
	Hazard index	4.9E-02	7.6E-02	1.1E-01	1.8E-01
6	Risk, upper bound slope factor	5.2E-07	8.0E-07	1.2E-06	1.9E-06
	Risk, lower bound slope factor	1.4E-07	2.2E-07	3.2E-07	5.2E-07
	Hazard index	2.5E-02	4.0E-02	5.9E-02	9.8E-02
7	Risk, upper bound slope factor	2.1E-08	5.7E-08	8.1E-08	1.3E-07
	Risk, lower bound slope factor	5.6E-09	1.6E-08	2.2E-08	3.5E-08
	Hazard index	2.4E-04	7.2E-04	9.9E-04	1.5E-03
8	Risk, upper bound slope factor	2.2E-06	3.4E-06	4.8E-06	7.3E-06
	Risk, lower bound slope factor	5.9E-07	9.2E-07	1.3E-06	2.0E-06
	Hazard index	9.9E-02	1.5E-01	2.2E-01	3.4E-01
9	Risk, upper bound slope factor	2.0E-06	3.2E-06	4.5E-06	6.9E-06
	Risk, lower bound slope factor	5.6E-07	8.6E-07	1.2E-06	1.9E-06
	Hazard index	7.7E-02	1.2E-01	1.7E-01	2.6E-01
10	Risk, upper bound slope factor	2.0E-06	3.0E-06	4.3E-06	6.7E-06
	Risk, lower bound slope factor	5.3E-07	8.2E-07	1.2E-06	1.8E-06
	Hazard index	5.9E-02	9.2E-02	1.3E-01	2.0E-01
11	Risk, upper bound slope factor	1.9E-06	2.9E-06	4.2E-06	6.6E-06
	Risk, lower bound slope factor	5.1E-07	8.0E-07	1.1E-06	1.8E-06
	Hazard index	4.2E-02	6.5E-02	9.2E-02	1.4E-01
12	Risk, upper bound slope factor	1.8E-06	2.9E-06	4.2E-06	6.7E-06
	Risk, lower bound slope factor	5.0E-07	7.9E-07	1.1E-06	1.8E-06
	Hazard index	2.6E-02	4.1E-02	5.9E-02	9.2E-02
13	Risk, upper bound slope factor	1.8E-06	2.8E-06	4.1E-06	6.7E-06
	Risk, lower bound slope factor	4.9E-07	7.7E-07	1.1E-06	1.8E-06
	Hazard index	1.1E-02	1.7E-02	2.5E-02	4.1E-02
64 oz	Risk, upper bound slope factor	8.3E-07	1.0E-06	1.3E-06	1.9E-06
	Risk, lower bound slope factor	2.3E-07	2.9E-07	3.6E-07	5.2E-07
	Hazard index	1.0E-02	1.3E-02	1.6E-02	2.2E-02

Table 8—Contribution to variance for parameters in probabilistic analysis.

	Scenario													
Parameter	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**64 oz**
C original formulation	0.79	0.79	0.78	0.77	0.75	0.69		0.79	0.78	0.77	0.75	0.72	0.70	
C new formulation							0.72							
C 64-oz formulation														0.13
IR	0.11	0.11	0.11	0.11	0.11	0.11	0.10	0.11	0.11	0.11	0.10	0.10	0.10	0.31
EF	0.08	0.08	0.08	0.08	0.08	0.08	0.07	0.08	0.08	0.08	0.08	0.07	0.07	0.23
BW 12 to 13				0.02	0.03	0.12								
BW 13 to 14				0.01	0.03									
BW 14 to 15														
BW 15 to 16														
BW 16 to 17														
BW 17 to 18														
BW adult							0.11		0.02	0.04	0.07	0.10	0.13	0.32

is worth noting that benzene was detected in 64-oz formulations, which were available at several of the stores visited during sampling activities. The potential contribution of consumption of the 64-oz product cannot be discounted as another potential source of exposure in this context. Samples of CLSCO were collected only in the¿ Houston area. Given that exposure to the environment (that is, elevated temperatures) during the storage, distribution, and handling of the product may contribute to the formation of benzene, the levels measured in CLSCO samples from the Houston area may not be representative of other parts of the country.

Discussion

To date, interpretation of the potential health implications of the benzene levels measured in a variety of soft drinks and other beverages has been based solely on comparison to the federal drinking water standard for benzene in drinking water of 5 ppb. The USEPA drinking water standard is based on an extrapolation from the inhalation toxicity criteria for benzene and is described in the USEPA Drinking Water Criteria Document for Benzene (USEPA 1985). Their calculation includes derivation of an air concentration of 4E-4 ppm as a threshold dose, based on review of 3 epidemiology studies of workplace cohorts. A respiratory absorption coefficient of 50% and the standard estimate of respiratory rate (20 m^3/d) were also employed in their calculation. Ultimately, the calculation yields an intake estimate of 13.5 μg/d. Based on the assumption that an individual consumes 2 L of water/d and weighs 70 kg, this yields an acceptable intake in water of 6.7 ppb. The MCL was ultimately set at 5 ppb as this was determined to be the lowest level that water systems can reasonably be required to remove should it occur in drinking water.

It is important to note that ingestion rate assumed in this calculation (2 L/d) is equivalent to drinking more than 4 bottles of CLSCO per day, an unrealistic amount for most consumers. The EPA Exposure Factors Handbook (Table 3-14) indicates a mean intake of 0.057 L/d for "Fruit Drinks," with a 99th percentile of 0.49 L/d. Similarly, a mean intake of 0.065 L/d is given for "Fruit Drinks and Ades" (Table 3-21), which is noted to include "regular and low-calorie fruit drinks, punches, and ades." The Total Diet Study conducted by the CSFAN at the FDA estimated consumption of drinks of this type ("Fruit Drink [10% juice], canned or bottled") at 0.041 L/d (USFDA 2001). While CLSCO may not fit perfectly into this beverage category, it is reasonably close. Further, the beverage with the highest rate of consumption was coffee (0.22 L/d), followed by carbonated beverages (0.17 L/d), both of which are substantially below the 2 L/d ingestion rate employed by USEPA in the development of the MCL. The consumption rates used in point estimate calculations was 0.473 L/d, while the consumption rates used in the probabilistic analyses were based on a triangular distribution and ranged from 0.43 to 0.95 L/d, all of which are appreciably lower than the 2 L/d ingestion rate used to develop the MCL.

Madl and Paustenbach (2002) summarize levels of benzene to which individuals may be exposed as a result of smoking cigarettes, pumping gasoline, or living in Los Angeles. As reported by the authors, cigarette smoke contains 57 μg benzene per cigarette on average. An individual smoking 1 pack of cigarettes per day might be expected to inhale 570 μg of benzene daily, assuming 50% absorbed or retained. A resident of Los Angeles may expect to breathe air containing an average 15 parts per billion by volume (ppbv) benzene, and as much as 57 ppbv. Using the standard respiratory rate of 20 m^3/d and assuming 50% absorbed or retained, this would yield an average intake of 477 μg/d, ranging up to 2.29 mg/d. If an individual were to consume 2 bottles of the older CLSCO formulation containing the highest measured concentrations of benzene (140 μg/L), their total exposure to benzene by mass would be approximately 132 μg. Further, because this formulation was available for only 6 y, the overall benzene mass to which individuals might be exposed is insignificant relative to that associated with living in Los Angeles or smoking 1 pack of cigarettes per day over a lifetime.

Conclusions

For the various exposure scenarios discussed here, which involve intake of benzene in soft drinks, our risk assessment indicates that both the cancer and noncancer hazards are less than the protective health benchmarks established by USEPA (acceptable cancer risk range of 1E-4 to 1E-6 and a HI of 1.0), regardless of the exposure scenario evaluated. As such, intake of benzene at the levels measured in the CLSCO products sampled during the course of this study is not expected to pose an unacceptable health threat under these conditions of exposure. The highest cancer risks estimated based on the exposure scenarios and assumptions described here are generally consistent with the risks associated with drinking water at the MCL. The drinking water unit risk values available on USEPA's Integrated Risk Information System (IRIS) of 4.4E-7 to 1.6E-6 per μg/L yield cancer risk estimates of 2.2E-6 and 8E-6, respectively. The highest point estimate cancer risk was determined to be 5.4E-6, while the central tendency (50th percentile) and upper bound (95th percentile) risk estimates determined in our probabilistic analyses were 3.7E-6 and 8.0E-6, values that are in line with the cancer risk associated with drinking water at the MCL.

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