Introduction
Arsenic and fluorine are elements that form organic and inorganic compounds ubiquitously present in nature. Living organisms are mainly exposed to inorganic arsenic and inorganic fluoride through food and water; thus, this study focuses on environmental exposure to inorganic arsenic and inorganic fluoride. The contamination of groundwater by arsenic and fluoride is common in arid and semi-arid regions of the world, especially in oxidized and alkaline environments of several countries, mainly from Latin America, Asia, and Africa. Over 300 million people worldwide use groundwater contaminated with arsenic or fluoride as a source of drinking water. The occurrence of arsenic or fluoride in groundwater is primarily ascribed to geogenic processes. These natural sources are usually related to the dissolution of arsenic- or fluorine-containing minerals present in rocks and soils. Mining activity, smelting operations, and burning of coal are the main anthropogenic sources of arsenic and fluoride.

Children are the most vulnerable and sensitive group; in utero exposure is a recognized condition of vulnerability. However, the total number of children exposed to arsenic or fluoride or concurrent exposure to both elements through drinking water in Mexico has not been clearly determined.

Methods
Estimation of Mexican Children Exposed to Arsenic and Fluoride

Data of water quality were obtained from the Inventario Nacional de Calidad del agua (INCA) [1] during sampling campaigns of underground wells carried out from 2005 to 2016. Localities were established according to the georeferencing data of the sampling site. Each site was verified using the national Water Geographic Information System (SIGA) [2]. Sites whose water use corresponded to public services, industrial use, or agricultural production areas located more than 300 meters away from a population were excluded. Sites where arsenic or fluoride was

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relevant for child exposure were considered as follows: arsenic $\geq 10$ $\mu$g/L and fluoride $\leq 1.5$ mg/L. The localities were considered only if the concentration of fluoride was $\geq 1.5$ mg/L and arsenic $< 10$ $\mu$g/L. Localities with co-exposure were included if the values of arsenic and fluoride exceeded the concentrations mentioned above. The number of individuals between 0 and 14 years of age was considered as the child population. Sites were represented using Quantum GIS [3] and maps obtained from Instituto Nacional de Estadística y Geografía (INEGI) [4]. The population exposed was estimated using the 2010 census at the INEGI for each locality enlisted [4]. Our estimation of exposed child population may be larger because the child population has increased since 2010.

**Biomonitoring Equivalents (BE)**

This review was performed considering those studies that reported levels of arsenic and fluoride in drinking water, urinary quantification of speciated arsenic (inorganic arsenic and its methylated metabolites), and urinary fluoride levels in child populations. For BE values, urinary arsenic and fluoride concentrations reported in child populations were revised.

**Results**

**Overview of Arsenic Exposure in Mexico and Its Health Effects**

The World Health Organization (WHO) recommends 10 $\mu$g/L as the maximum level of arsenic in drinking water [5]; however, in Mexico, the guideline value is 25 $\mu$g/L (Table 1) [6]. There are many regions in Mexico where the natural concentration of arsenic in the groundwater depends on the arsenic content of the bedrock; here, the levels of arsenic in drinking water are higher than the recommended limit of 10 $\mu$g/L (Figure 1) and higher than Mexico’s limit 25 $\mu$g/L. We estimated that approximately 500,000 children up to 14 years of age drink water with arsenic levels over 10 $\mu$g/L, around 205,000 of them drink water with 25 $\mu$gAs/L, and approximately 17,500 children are at higher risk because their drinking water contains between 75 and 500 $\mu$gAs/L. The additional child population *in utero* was not included in this estimation.

The general population is exposed to arsenic by drinking water, eating food, or consuming soil polluted with high levels of arsenic.

**Health Effects**

Arsenic accumulates mainly in the skin, causing cutaneous alteration; changes in pigmentation and hyperkeratosis are the best described and characterized toxic signs of chronic exposure to arsenic, mostly in the adult population. However, skin changes were documented in children 6 to 8 years old. Other adverse effects described in children are genetic damage, impaired learning and memory abilities, neuropathies, cardiovascular alterations, endocrine dysfunctions, and immunosuppression [24].

**Neurotoxic Effects**

In San Luis Potosí, children’s verbal skills, long term memory, and linguistic abstraction were negatively associated with increased levels of arsenic in urine [25]. In the Laguna region, the most-studied area, neurotoxic effects of arsenic, such as impaired cognitive and behavioral functions,
were described in a child population of approximately 600 children between 6 and 8 years of age [26–27]. In Durango state, arsenic exposure was also associated with impaired cognitive abilities [28].
Immunotoxic Events
At the Zimapán area, children 6 to 12 years old showed impaired immune function, allergies, and altered cellular proliferation [29]. Also, there are studies documenting immunosuppression [30] and chronic inflammation biomarkers. In the Laguna region, a study including 275 children showed 58% having a restrictive spirometric pattern, while the highest exposed group showed arsenic-induced alterations in inflammatory biomarkers. The authors suggest that chronic inflammation might contribute to the development of restrictive lung diseases that could start in utero [31–32].

Genotoxicity
Genetic damage is considered a biomarker of cancer risk. Arsenic is a genotoxic agent. Similar to adults, children showed genetic damage associated with arsenic exposure [33–35]. Epigenetic changes were observed in cord-blood cells [32, 36–38] and in leukocytes from child populations exposed to arsenic in drinking water [39] or in historic mining areas [40].

Cardiac and Renal Effects
At the Zimapán area, studies identified a higher risk for cardiac diseases such as atherogenesis, arterial hypertension, cardiac hypertrophy, and dysfunction [41–42]. In Villa de Reyes, San Luis Potosí, children showed early signs of kidney damage [43].

Overview of Fluoride Exposure in Mexico and Its Health Effects
Drinking water is the major contributor to fluoride exposure. In children, this source contributes 60% to 80% of total daily fluoride intake [44]. Water fluoride regulation values are shown in Table 1. Mexico’s limits are 1.5 mg/L in tap water, 0.7 mg/L in bottled water, and 2 mg/L in natural mineral water [6, 10]. In Figure 1, the presence of high natural fluoride levels in Mexico’s tap water are shown. We estimated that in Mexico approximately 6 million children up to 14 years of age drink water with fluoride levels over 1.5 mg/L and approximately 400,000 children are at higher risk because their drinking water exceeds 4.5 mg/L. In these estimations, we did not consider pregnant women for in utero exposure.

Fluoride toothpaste use has been one of the most common strategies to prevent dental caries in Mexico and worldwide. Studies have reported that between 49.8% to 90.9% of children 6 to 13 years old use fluoride toothpaste at least once a day [45]. Toothpaste fluoride concentrations for children in Mexico varied from nondetectable to 1153 mg/Kg, with an average of 563 ± 350 mg/Kg [46]. These large variations are due in part to the lack of an official regulation and nonmandatory normativity [47]. Children younger than 6, especially those not supervised by an adult, are at higher risk of developing dental fluorosis due to ingesting excessive dental products. Mexican regulations have established the use of a pea-sized portion of toothpaste with 550 mg/Kg of fluoride concentration under adult supervision for children from 2 to 6 years. Excessive quantities and adult toothpaste (1000 mg/Kg of fluoride) use by children under 6 was reported [48]. Moreover, an increase in dental fluorosis associated with ingesting dental products has been reported in Mexican children 11 to 12 years old [49]. It has been estimated that toothpaste can contribute at least 20% of the total fluoride exposure in children [50].

Fluoride Enriched Supplements
Since 1940, the Pan American Health Organization has proposed fluoride food enrichment in zones with low fluoride water concentrations to prevent tooth decay. A dose of 0.05 mg/Kg per day was proposed to prevent tooth decay in children. However, evidence suggests that the predominant caries-preventive effect of fluoride is by its topical rather than systemic effect [51]. In Mexico, a salt fluoridation program to prevent tooth decay was introduced in some states in 1991. Mexican regulation establishes 250 mg/Kg of salt (Table 1) [19]. This regulation establishes no fluorinated salt distribution in zones with natural water fluoride concentrations above 0.7 mg/L to protect the population from dental fluorosis. However, 39% to 69% of children (n = 475) from areas with fluorinated salt distribution and exposure to optimal fluoride concentrations (0.7 and 1.5 mg/L) in drinking water showed dental fluorosis [52].

Besides drinking water and dental products, food can contribute up to 20% of total daily fluoride intake. The most important foods in terms of potential contribution to fluoride exposure are infant formula, commercial beverages such as juice and soft drinks, grapes and grape products, teas, and processed chicken. Infant formula and commercial beverages greatly depend on the fluoride content of the water used in their preparation [44]. Consumption of soft drinks and sweetened beverages has been reported in up to 79% of Mexican children [53]. Also, fluoride concentrations above 0.7 mg/L were reported in bottled beverages such as water, juices, nectars, and soft drinks consumed in some regions [54].

Soil could be an additional source of fluoride exposure for children. A study performed in the Laguna region reported soil fluoride concentrations between 89.75 to 926.63 mg/Kg, and the estimated percentage of bio-accessible fluoride from this source was between 2% and 46% [23]. The estimated value for incidental soil ingestion by a 20 Kg child with no pica habit is 100 mg/day. Nevertheless, fluoride intake due to soil has not been considered.

Health Effects
Worldwide, excessive fluoride ingestion has been associated with dental and skeletal fluorosis and nonskeletal adverse effects, such as neurocognitive alterations, thyroid dysfunction, kidney injury, and cardiovascular alterations.

Dental and Skeletal Fluorosis
Dental and skeletal fluorosis is the most common adverse effect associated with chronic fluoride exposure. Dental fluorosis cases are characterized by a hypomineralization of the enamel surface [55]. The prevalence of dental fluorosis in Mexico has been evaluated in several studies. A study review including 14 child population studies published from 1979 to 2001 observed a den-
tal fluorosis prevalence range from 30% to 100% [56]. Another review that included 17 studies performed in Mexican communities from 10 states between 2005 and 2015 reported a prevalence range of 15.5% to 100% [57]. This high prevalence even in regions considered to have optimal or suboptimal fluoride concentrations suggests an important contribution from other sources, which should be considered in a reevaluation of the concept of optimal fluoride concentration in water. A reduction of the optimal fluoride concentration in drinking water to 0.7 mg/L has been proposed [9]. Skeletal fluorosis, which is a bone disorder characterized by an increased bone mass and radiographic density, have not been reported in Mexican children.

**Neurodevelopmental Toxicity**

One of the most nonskeletal adverse effects studied in fluoride-exposed children is cognitive dysfunction. In endemic fluorosis regions, children who live in areas with high fluoride exposure reported lower IQ scores [58]. Similarly, a cross-sectional study of 132 Mexican children reported an association between fluoride exposure and reduced cognitive, verbal, and full IQ scores [28]. The main windows of susceptibility for neurodevelopmental toxicity are in utero, infancy, and early childhood. In a longitudinal birth cohort study, fluoride in maternal urine in the first (1.9 mg/L) and second (2.0 mg/L) trimesters was negatively associated on the mental development index in Mexican infants 3 to 15 months old, suggesting neurodevelopmental adverse effects due to fluoride exposure [59].

**Endocrine Disruption**

Fluoride is considered as a possible endocrine disruptor. Studies reported a decrease in circulating thyroid hormones (Free T4 or thyroid stimulating hormone) in children exposed to high natural fluoride levels in drinking water in India (1.6 to 5.5 mg/L) and China (mean 2.36 ± 0.7 mg/L) [60–1]. In Mexico, there are no studies on fluoride exposure and thyroid function in children.

**Early Kidney Injury**

The kidneys are susceptible to fluoride exposure damage. Ecological studies reported a relationship between environmental fluoride levels and chronic kidney disease of uncertain etiology [62]. However, limited information from epidemiological studies is available in part due to the lack of human early kidney injury biomarkers. In 2007, a study performed in China reported a significant increase in two early kidney injury biomarkers in children exposed to 2 mg/L of fluoride in drinking water, suggesting early injury by fluoride exposure [63]. Because evidence is limited, more studies are required to assess kidney injury due to fluoride exposure.

**Cardiovascular Diseases (CVD)**

Atherosclerosis, hypertension, and cardiac dysfunction in adults are associated with fluoride exposure [64]. In children, limited information is available about the effects of early fluoride exposure. A child study performed in Turkey reported an increased electrocardiographic Q-T interval, suggesting a vulnerability for children developing arrhythmias [65]. Thus, more studies are necessary to assess the effect of fluoride in CVD development.

**Potential Co-exposure of Arsenic and Fluoride**

The co-occurrence of high arsenic and fluoride levels in drinking water has been reported in many geographical regions. In Mexico, around 40% of localities with arsenic levels higher than 10 µg/L also present concurrent fluoride exposure higher than 1.5 mgF/L, especially in the central and northern regions of the country (Figure 1). Little is known about the adverse health effects from long-term exposure to arsenic and fluoride at low and high doses. The concurrent exposure may lead to a network of both synergistic and antagonistic interactions that could represent a serious health risk. Thus, the potential role of fluoride in health effects previously attributed to arsenic alone should be systematically studied.

**Biomonitoring Equivalents (BE) for Arsenic**

The current standards and guidelines of safe exposure to arsenic are summarized in Table 1. The reference dose (RfD) for arsenic is 0.0003 mg/Kg-d, the no-observed-adverse-effect and lowest-observed-adverse-effect levels were derived from this value. Additionally, it corresponds to the total daily intake (TDI) and the minimum risk level for chronic exposure.

Food sources, especially rice-based products, are increasingly recognized as a source of arsenic exposure for children [73]. New regulations set arsenic content in rice products for infants and young children to 0.1 mg/Kg (Table 1).

Because children engage in frequent hand-to-mouth behaviors and live and play close to the ground, they are generally more likely to have higher exposure to soil contaminants. The Canadian soil quality guideline is one of the most restrictive at 12 mg/Kg (Table 1) [22]. In Mexico, the guideline established 22 mg/Kg as the action level for arsenic contaminated soil (Table 1) [20].

**Toxicokinetics of Arsenic in Children**

Arsenic is absorbed primarily through oral ingestion or inhalation. Absorption differences between children and adults have not been reported. Absorbed arsenic binds to red blood cells, may pass through the placenta, and deposits itself in the liver, kidneys, urinary bladder, muscle, brain, bone, hair, skin, and nails. Arsenic metabolism is a process that begins with arsenate, which is converted into arsinite for its methylation into monomethylated (MAs) and dimethylated (DMAs) arsenicals, before being excreted in the urine. Arsenic urine concentrations in children are typically higher than adults exposed to the same concentrations, suggesting children accumulate less arsenic due to the activity of their metabolism, which is different from adults [74–75]. Children might have higher arsenic methylation than adults within a certain range of arsenic exposure concentrations [75]. In relation to sex, boys present higher arsenic levels in urine and less ability to methylate arsenic than girls [76].
Table 2: Exposure Guidelines Values for Oral Exposure to Arsenic and Fluoride.

| Organization | Guideline, Criteria (year of evaluation) | Study Description | Endpoint and Dose | Value | Experimental Doses (mg/Kg-day) |
|--------------|------------------------------------------|-------------------|-------------------|-------|-------------------------------|
| **Arsenic Non-Cancer Endpoints** | | | | | |
| US EPA Health Canada [66] | RfD (1993), TDI (2008) | Human cohort exposed to arsenic in drinking water | Hyperpigmentation, keratosis, and ar complications | 0.0003 mg/Kg-d | NOAEL: 0.0008 LOAEL: 0.014 |
| ATSDR [66] | MRL, chronic (2007) | Human cohort exposed to arsenic in drinking water | Dermal effects in a farming population | 0.0003 mg/Kg-d | NOAEL: 0.0008 |
| ATSDR [67] | MRL, acute (2007) | Human cohort exposed to contaminated soy sauce | Facial edema and gastrointestinal effects | 0.005 mg/Kg-d | LOAEL: 0.05 |
| US EPA [68] | Ingestion SL Child THQ = 1 (2017)* | | | 0.39 mg/Kg | |
| **Arsenic Cancer Endpoints** | | | | | |
| US EPA [66] | OSF (2007) | Human cohort exposed to arsenic in drinking water | Skin cancer | 1.5 mg/Kg-d | |
| **Fluoride Non-Cancer Endpoints** | | | | | |
| US EPA [69] | RfD, chronic (2010) | Cross-sectional study in children exposed to fluoride in drinking water | Severe dental fluorosis | 0.08 mg/Kg-d | NOAEL: 0.08 |
| ATSDR [70] | MRL, chronic (2003) | Cross-sectional study in adult Chinese population exposed to fluoride in drinking water | Risk of bone fractures | 0.05 mg/Kg-d | NOAEL: 0.15 |
| Health Canada [71] | TDI, chronic (2010) | Cross-sectional study in children exposed to fluoride from fluids and food | Moderate dental fluorosis | 0.105 mg/Kg-d | NOAEL: 0.105 |
| IOM [72] | UL, children under 8 years (1997) | Studies in children exposed to fluoride from dietary sources | Moderate dental fluorosis | 0.1 mg/Kg-d | LOAEL: 0.1 |
| | UL, children ≥ 8 years (1997) | Early signs of skeletal fluorosis | 10 mg/day | NOAEL: 10 mg/day |

**Abbreviations:** RfD, reference dose; TDI, total daily intake; MRL, minimum risk level; SL, screening level; THQ, target hazard quotient; OSF, oral slope factor; UL, upper intake; NOAEL, non-observable adverse effect level; LOAEL, low-observable adverse effect level.

* Non-Cancer Child Hazard Index (HI) = 1.
Derivation of Biomonitoring Equivalents
A BE represents the concentration of a chemical or its metabolite(s) in biological specimens compared to an acceptable level of exposure based on existing exposure guidelines values (e.g., a RfD, MRLs, or TDI) [77]. A BE is derived by integrating available data on toxicokinetics with the health-based exposure guidelines to quantitatively interpret population-based biomonitoring results in a public health risk context [77]. The BE value for urinary arsenic, which is the sum of inorganic arsenic and its methylated species, is 6.4 µg/L (8.3 µg/g creatinine) [78]. This BE is derived from recent available health-based exposure guidance values (risk-specific doses for cancer endpoints) from several international agencies and the integration of controlled human dosing toxicokinetic data (urine excretion) [78]. Hence, the arsenic BE is derived for the simple exposure scenario of continuous steady-state exposure. Comparisons to this BE value should be made only with the sum of inorganic arsenic + MAs + DMAs. Hays et al indicate that biomonitoring results above the point of departure BE (BE\textsubscript{POD} = 19.3 µg/L or 24.9 µg/g creatinine) should be considered as high priority for risk assessment follow-up [78].

The German reference value (RV\textsubscript{G}) established for children (3 to 14 years old) who did not eat fish 48 hours prior to sample collection has a similar derivation strategy, but RV\textsubscript{G} is equal to 15 µg/L and is within the 95% confidence interval of the 95th percentile of the concentration of urine arsenic in a reference population sampled in the German Environmental Survey [79]. Hence, 15 µg/L represents the body burden of arsenic in a representative population from Germany and can be used only as an indicator of higher-than-usual internal exposure levels and knowing that it is linked to a specific country or region [79].

Biomonitoring Equivalents for Fluoride

Exposure Guidance Values
Health-based noncancer fluoride guidance values have been reported by many agencies (Table 2). These values are based on objectionable fluorosis (moderate to severe) and skeletal fluorosis as a disease criterion. However, most of these events appear in high doses of exposure and might not be adequate for infants and younger children (3 to 6 years old) who are at highest risk due to their body mass, high ingestion of dental products, and metabolism [44]. Further, other nonskeletal adverse effects, such as neurocognitive dysfunction, can occur at low doses of exposure, which can be useful as a disease criterion [80].

Many sources of fluoride contribute to TDI. National and international environmental quality standards have been established (Table 2). In Mexico, regulations are available only for water and salt, which establish the exclusive distribution of fluorinated salt in regions with fluoride water concentrations under 0.7 mg/L [19].

Toxicokinetics of Fluoride in Children
Fluoride is mainly absorbed through the gastrointestinal tract. No absorption differences between adults and children have been reported. However, studies suggest that factors such as undernutrition status and low water concentration of some ions, such as Ca\textsuperscript{2+}, Mg\textsuperscript{2+}, and Al\textsuperscript{3+}, can increase fluoride absorption and bioavailability [81]. Fluoride is rapidly distributed by the bloodstream to soft tissues, is readily transferred across the placenta, and accumulates mainly in mineralized tissues such as bones and teeth. Fluoride retention is 20% higher in growing children than adults, mainly due to a higher fluoride uptake in developing bones [70]. Urine is the main route of fluoride excretion. Lower urinary fluoride excretion has been reported in children, because children present the highest accumulation in calcified tissues and the highest urine flow rates [82].

Derivation of Biomonitoring Equivalents
Potential sources of fluoride exposure have been described above. Estimation of TDI requires their identification and exposure magnitude, frequency, and duration [83]. Urinary fluoride concentration is a biomarker of fluoride exposure, mainly due to the significant correlation with fluoride intake and the low invasiveness of sample collection [44]. However, no reference values (RV) for environmentally exposed populations have been established. Recently, Aylward et al. reported BE for fluoride [84]. These values can be calculated using data from studies that relate urinary fluoride excretion to daily fluoride intake and estimated body-weight adjusted daily urinary volume or creatinine excretion in children.

Children Biomonitoring Reference Values for Arsenic and Fluoride
Table 3 shows biomonitoring data of urinary arsenic in children from nonendemic populations around the world. They represent general worldwide background RV of arsenic in children. In general, the 95th percentile of the sum of arsenical concentrations is <20 µg/L, both corrected or not, for urine dilution. All data are below the German Biological Tolerance Value (BAT = 50 µg/L) and the Biological Exposure Index (BEI\textsuperscript{®} = 35 µg/L); both RV for adults are in occupational settings for German and US agencies, respectively. Most of the studies presented in Table 3 present levels higher than the BE (6.4 µg/L). Importantly, the average of the 50th percentile of arsenic concentrations in endemic regions of Mexico is around 80 µg/L, higher than BE, RV\textsubscript{A}, BEI\textsuperscript{®}, or BAT (Table 4).

Urinary fluoride BE values for children have been reported [84]. Based on the guidance value reported by USEPA (RfD = 0.08 mg/Kg-day), a BE value of 1.0 mg/L for children ages 3 to 6 and 1.2 mg/L for children ages 6 to 10 have been proposed. Biomonitoring data of urinary fluoride in children from nonendemic fluoride regions have been reported in some countries (Table 3). The mean levels and 50th percentiles of urinary fluoride concentrations reported by those studies are below BE value for fluoride (1.2 mg/L), including Mexico. However, 95th and 75th percentile values reported from Canada and China present urinary fluoride levels above BE value. In general, low fluoride concentrations in water (<1.5 mg/L) were reported for these nonendemic fluoride regions; however, water fluoridation programs have been applied for Canada and the United Kingdom, and alternative sources of fluoride exposure could have also occurred.
### Table 3: Human Biomonitoring Data of Arsenic and Fluoride in Urine from Surveys in Children from Non-endemic/Reference Populations.

#### Arsenic Biomonitoring

| Country/Ref                          | n   | Age (years) | Total As | SumAs                  | iAs          | MAs           | DMAs           | Urine Dilution Adj       |
|--------------------------------------|-----|-------------|----------|------------------------|--------------|---------------|-----------------|---------------------------|
| Canada, Health 2014–2015 [71]        | 513 | 6–11        |          | 95th: 18 µg/L          | 95th: 1.4 µg/L | 50th: <LOD    | 50th: 3.7 µg/L | None                      |
| Germany [85]                         | 1734| 3–14        |          | 95th: 14 µg/L          |              | 50th: <LOD    |                 | None                      |
| Asaluyeh City, Iran [86]             | 368 | 6–12        |          | C: 3.0 µg/gCr          |              |               |                 | Urinary Creatinine        |
| Yucatán, México [87]                 | 36  | 6–9         |          | 7.5 µg/L               |              |               |                 | None                      |
| Yucatán, México [88]                 | 107 | 6–9         |          | 2.9 µg/L               |              |               |                 | None                      |
| Montevideo, Uruguay [89]             | 327 | 5–9         |          | 9.9 µg/L               | 1.0 µg/L     | 0.9 µg/L      | 1.9 µg/L       | Specific Gravity          |
| Asturias, Gipuzkoa, Sabadell and Valencia, Spain [90] | 400 | 4           |          | 0.3 µg/L               | 0.4 µg/L     | 3.9 µg/L      |                 | Specific Gravity          |
| Huelva, Spain [91]                   | 261 | 6–9         |          | 95th: 20.8 µg/gCr      | 95th: 1.7 µg/gCr | 50th: <LOD    | 50th: 4.6 µg/gCr | Urinary Creatinine        |
| US, NHANES 2011–2014 [92]            | 397 | 6–12        |          | 95th: 17.8 µg/gCr      | 95th: 13.3 µg/gCr | 50th: <LOD    | 50th: 4.6 µg/gCr | Urinary Creatinine        |
| US, NHANES 2003–2008 [93]            | 2323| 6–17        |          | 95th: 8.9 µg/gCr       | 95th: 1.21 ± 0.6 mg/gCr | 50th: <LOD    | 50th: 4.6 µg/gCr | Urinary Creatinine        |
| US, NHANES 2003–2004 [94]            | 290 | 6–11        |          | 95th: 38.2 µg/gCr      | 95th: 14.7 µg/gCr | 50th: <LOD    | 50th: 4.0 µg/gCr | Urinary Creatinine        |

#### Fluoride Biomonitoring

| Country/Ref                          | n   | Age/years | Source of Exposure | F Drinking water | F in urine | Urine Dilution Adj |
|--------------------------------------|-----|----------|--------------------|-------------------|------------|-------------------|
| Trinidad and Tobago 2001 [95]        | 500 | 6–14     | NR                 | NR                | Mean: 0.57 mg/L | None              |
| Iztapalapa, Mexico City [96]         | 205 | 4–5      | Various            | 0.27 mg/L         | Mean: 0.84 mg/L | None              |
| China 2008–2009 [97]                 | 26931| 8–12     | Drinking Water     | 0.54 mg/L         | 50th: 0.90 mg/L | None              |
| Health Canada 2014–2015 [71]         | 533 | 6–11     | Various            | NR                | 95th: 1.6 mg/L | None              |
| United Kingdom 2002–2014 [98]        | 158 | 1.5–7    | Various            | NR                | Mean: 1.21 ± 0.6 mg/gCr | Urinary Creatinine |

**Abbreviations:** SumAs, sum of arsenic; C, case; R, reference; F, fluoride; NR, non-reported

**Notes:** Total As includes all As species, organic and inorganic, whereas SumAs are: As(II) + As(V) + MAs + DMAs.
**Table 4:** Summary of Recent Human Biomonitoring Data and Health Effects Associated with Arsenic and Fluoride Exposure in Children from Endemic Regions in Mexico.

### Arsenic Biomonitoring

| Region/Ref | n   | Age (years) | SumAs | iAs  | MA  | DMA | Urine Dilution Adj. | Health Effect(s) |
|------------|-----|-------------|-------|------|-----|-----|---------------------|------------------|
| Torreón, Coahuila [76] | 591 | 6–8 | 52.1 µg/L | 7.3 µg/L | 6.4 µg/L | 38.2 µg/L | None | Reducing As Methylation Capacity |
| Torreón, Coahuila [27] | 526 | 6–7 | 55.2 µg/L | 7.5 µg/L | 6.7 µg/L | 39.3 µg/L | None | Poor Behavior |
| Torreón, Coahuila [26] | 591 | 6–8 | 58.1 µg/L | 8.7 µg/L | 7.7 µg/L | 41.7 µg/L | None | Cognitive Deficits |
| Ciudad Juárez, Chihuahua [119] | 135 | 6–12 | 59th: 48.9 µg/gCr | 50th: 17.6 µg/gCr | 40.7 µg/L | None | Urinary Creatinine | Biomonitoring |
| La Laguna, Durango [32] | 358 | 6–12 | H: 294.0 µg/L | M: 143.7 µg/L | L: 84.9 µg/L | H: 51.6 µg/L | M: 23.9 µg/L | L: 18.4 µg/L | Urinary Creatinine | Decreased Lung Function |
| Táxico, Guerrero [99] | 50 | 6–10 | 16.5 µg/L | None | None | None | Biomonitring | |
| Zimapán, Hidalgo [41] | 195 | 3–14 | 59.1 µg/L | 5.4 µg/L | 5.4 µg/L | 46.7 µg/L | None | Early Cardiovascular Effects |
| Zimapán, Hidalgo [100] | 87 | 6–10 | 194.6 µg/gCr | 20.4 µg/gCr | 30.1 µg/gCr | 144.1 µg/gCr | Urinary Creatinine | Oxidative Stress |
| Zimapán, Hidalgo [29] | 90 | 6–10 | 186.7 µg/L | 19.9 µg/L | 28.5 µg/L | 135.7 µg/L | None | Immunosuppression |
| Villa de la Paz and Morales, San Luis Potosí [40] | 84 | 6–12 | 26.44 µg/gCr | 19.9 µg/gCr | 28.5 µg/L | 135.7 µg/gCr | None | Urinary Creatinine | Epigenetic Imbalance |
| Villa de Reyes, San Luis Potosí [43] | 83 | 5–12 | 37.4 µg/L | None | None | None | Early Kidney Damage |
| Highlands and Centre regions, San Luis Potosí [34] | 85 | 4–11 | H: 44.5 µg/gCr | M: 16.8 µg/gCr | L: 12.8 µg/gCr | H: 40.7 µg/L | M: 19.6 µg/L | L: 10.8 µg/L | Urinary Creatinine | DNA Damage |
| Yaqui and Mayo Valleys, Sonora [101] | 165 | 6–12 | 30.9 µg/L | None | None | None | Biomonitring | |

### Fluoride Biomonitoring

| Country/Ref | n   | Age (years) | Source of Exposure | F Drinking Water | Fin urine | Urine Dilution Adj. | Health Effect(s) |
|-------------|-----|-------------|--------------------|------------------|------------|---------------------|------------------|
| Hermosillo, Sonora [102] | 31 | 8–9 | Drinking Water and Food | L: 0.54 mg/L | M: 0.78 mg/L | H: 2.77 mg/L | L: 0.93 mg/L | None | Risk Assessment |
| L: Moctezuma, San Luis Potosí M: Salitral, San Luis Potosí H: 5 de Febrero, Durango [28] | 132 | 6–10 | Drinking Water | L: 0.8 mg/L | M: 5.3 mg/L | H: 9.4 mg/L | L: 1.8 mg/gCr | Urinary Creatinine | Cognitive Deficits |

(Contd.)
| Region/Ref                                      | n  | Age (years) | Source of Exposure | F Drinking water | Fin urine | Urine Dilution Adj. | Health Effect(s)                           |
|------------------------------------------------|----|-------------|--------------------|------------------|-----------|----------------------|--------------------------------------------|
| Soledad de Graciano Sánchez, San Luis Potosí [103] | 20 | 6–12        | Drinking Water     | 0.67 mg/L        | 1.94 mg/μCr|                      | Urinary Creatinine Increased Apoptosis in PBMC |
| Villa de Ramos, San Luis Potosí [104]          | 72 | 6–12        | Drinking Water     | 2.3–5.4 mg/L     | 1.0–8.0 mg/L| Specific Gravity     | Inflammatory Expression Genes              |
| Salinas de Hidalgo, San Luis Potosí [105]      | 111| 6–12        | Drinking Water     | 4.54 mg/L        | 3.14 ± 1.09 mg/L| Specific Gravity     | Dental Fluorosis Prevalence (95%)          |
| Villa de Reyes, San Luis Potosí [43]          | 83 | 5–12        | Drinking Water     | 2.47 mg/L        | 50th: 2.18 mg/L| None                | None                                       |

Abbreviations: SumAs, sum of arsenic; H, high; M, medium; L, low; NR, non-reported; PBMC, peripheral blood mononuclear cells.

Notes: Arsenic levels were quantified in urine samples. SumAs: As(III) + As(V) + MAs+ DMAs.
**Table 4** shows biomonitoring data of urinary fluoride in Mexican children from endemic fluorosis regions. However, most of these studies have been performed to investigate fluoride toxicity. In general, most urinary fluoride concentrations reported are above the BE value for fluoride (1.2 mg/L), even in regions with low fluoride concentration in the water. In Mexico, alternative sources of fluoride exposure, such as salt, toothpaste, soil, and food, can also occur. However, it is common to consider only one or two sources, which leads to the potential underestimation of fluoride exposure.

### Discussion

According to the information gathered, a conservative estimation put approximately 6.5 million children in health risk due to arsenic and fluoride exposure in Mexico. These child populations are at an increased risk for impaired neuronal development that might lead to lower learning abilities, higher susceptibility to infectious diseases and inflammation, and chronic conditions that are associated with cancer and degenerative diseases in adulthood.

Thus, using BE for urine samples constitutes a valuable tool for identifying child populations at risk. This is a relatively noninvasive methodology to identify exposure that could be implemented in the identified endemic regions. Also, if international regulatory measures are to be considered, operative guidelines should be established to make studies comparable on a global scale.

### Arsenic and Fluoride BE Values for Mexican Population

Urine is the more reliable biospecimen to assess arsenic and fluoride exposure. However, the values need to be adjusted for dilution due to the variable hydration status of the participants. Although adjustment by urinary creatinine is traditionally used, this could result in biased estimates because the urinary biomarker of exposure and creatinine excretion may be affected differentially due to physiological and pathophysiological conditions [106]. Urine specific gravity may be a more appropriate method for urine dilution adjustment in human biomonitoring studies.

The implementation of a global urinary RV for arsenic is challenging. BE and RV$_{0.9}$ are regional, well-established RV values for U.S. and German populations. Currently, there are no unexposed background RV or guidance values of arsenic in urine for the Mexican population. Arsenic levels in non-endemic regions, like Yucatan, Mexico, are below 10 µg/L and can be an approximation of how the RV could be for the Mexican population [87–88]. The BE of 6.4 µg/L proposed by Hays et al. cannot be realistically adopted by Mexico [78]. Hence, we propose adopting the RV$_{0.9}$ of 15 µg/L proposed by Schultz et al. [107]. Although the RV$_{0.9}$ represents the basal levels of urine arsenic for a specific country (Germany), it is an achievable RV, especially if the Mexican guideline for arsenic in drinking water is reduced to 10 µg/L. Finally, this tool could be used for large and local national biomonitoring studies to establish basal RV.

Limited worldwide biomonitoring data for fluoride was available. Aylward et al. proposed a BE value for urinary fluoride that considers fluoride excretion patterns in children and that can be used to assess fluoride exposure in child populations [84]. It is important to mention that this BE value is based on severe dental fluorosis as a disease criterion derived from a non-Mexican child population (Table 2). In Mexico, high dental fluorosis prevalence rates have been reported even in regions with fluoride water concentrations <1.5 mg/L, suggesting alternative sources of fluoride exposure [57, 71, 97]. Also, dose-response association between fluoride intake and dental fluorosis suggests that the critical limit in guidance values may not be safe for Mexican children and should be revised in further research to establish recommendations for fluoride distribution schemes and regulations in water, salt, food, and toothpaste in Mexico [96]. Many endemic-fluorosis regions in Mexico have been identified, and the mean urinary fluoride concentrations in some of them are around 2 to 3 mg/L (Table 4). However, no urinary RV or available data from nonendemic regions are reported, and most of the studies performed in Mexico that evaluate fluoride toxicity do not report urine fluoride concentrations. Considering the limited information in Mexico and the limited biomonitoring data from other nonendemic populations, we propose that a BE value of 1.2 mg/L be adopted as a reference to assess fluoride exposure in Mexican children. Nevertheless, as in the case of arsenic, future biomonitoring studies performed in Mexican populations are necessary to establish RV; furthermore, other nonskeletal diseases should be considered for BE derivation.

Although a majority of BE calculations are made assuming there are no differences between child and adult populations, considering cancer as the maximum adverse consequence to chronic exposure, this may not be the best option for the child population. Not all environmental insults lead to cancer; however, exposure to insults may create equally incapacitating health risks. Therefore, it is necessary to reconsider other noncommunicable diseases (NCD) in the derivation of BE, such as those related to neurotoxicity and immunotoxicity that are reported in various epidemiological studies in children (Table 4) [108].

### Cost of Exposure to Arsenic and Fluoride

Nearly two-thirds of deaths caused by environmental risk factors are due to NCD, such as obesity, diabetes, cardiovascular disease, chronic respiratory diseases, neurological diseases, and cancer [109–110]. Both arsenic and fluoride exposure have been linked to NCD [111–112]. NCD are considered a major risk to economic loss, and low-income and middle-income economies are highly vulnerable. In Argentina, Brazil, Colombia, and Mexico, the cumulative loss of gross domestic product from heart disease, stroke, and diabetes between 2006 and 2015 was $13.54 billion [113]. Thus, prevention of arsenic- and fluoride-related diseases, by minimizing exposure of highly vulnerable populations such as children and pregnant women, appears to be a reasonable strategy to reduce the high demand and cost in health services in the long term. For example, Nigra et al. assessed the health benefits of the U.S. reduction of arsenic in drinking water from 50 µg/L to 10 µg/L since 2006 [114]. Over a 10-year period, the levels of DMAs fell by 17%, and a reduction of 200 to 900 lung and bladder cancer cases per year was estimated, if this reduction remains across a lifetime, which also reduces health.
services costs. Also, in a cross-sectional study performed in Chinese children \((n = 26,931)\), a significant dental fluorosis rate reduction was reported after 10 years of safe fluoride drinking water supply \([97]\).

However, in the case of fluoride, it has been found in recent years that many populations across the world where fluoride exceeds the permitted levels, dental fluorosis has been observed. Moreover, this condition is now linked to other NCD, such as neurological or endocrine illness \([51]\). Ko and Thiessen estimated that in severe fluorosis children’s teeth need porcelain veneer treatments. If they are replaced every 12 years, the lifetime cost of veneers for a child with moderate or severe fluorosis would be at least $4,434 \([115]\).

Finally, disease estimation gives us another insight into the impact of exposure to arsenic and fluoride. For arsenic, cancers and skin lesions are commonly used as indicators. Worldwide, the burden of disease due to skin lesions caused by arsenic in drinking water ranges from 1.5 to 6.7 disability adjusted life years (DALYs) per 1,000 population \([116]\). Each year, 9,129 to 119,176 additional cases of bladder cancer; 11,844 to 121,442 cases of lung cancer; and 10,729 to 110,015 cases of skin cancer worldwide are attributable to inorganic arsenic in food \([117]\). For fluoride, the global burden of disease based on the exposure-response relationship for skeletal fluorosis ranges from less than 1 to 20 DALYs per 1,000 population \([118]\).

**Final remarks**

Given the potential adverse health effects related to arsenic and fluoride, immediate measures should be taken to reduce exposure, particularly for vulnerable populations and specifically for children and pregnant women.

The BE values presented here are proposed as a starting point for regulatory purposes; however, it is emphasized that these BE values will have to be adjusted as more information becomes available about individual exposure and co-exposure to arsenic and fluoride.

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**Competing Interests**

The authors have no competing interests to declare.

**Author Contributions**

Jorge H. Limón-Pacheco wrote the manuscript and performed the estimation of children exposed; Mónica I. Jiménez-Córdova and Mariana Cárdenas-González compiled information, made interpretation of dates, revised the manuscript, and contributed to the discussion; Ilse M. Sánchez Retana compiled information from databases; María E. Gonsebatt provided substantive inputs in the revision of the paper; and Luz M. Del Razo had primary responsibility for the final content. All authors read and approved the final manuscript.

**References**

1. **Inventory Nacional de Calidad del Agua (INCA).** Inventory Nacional de Calidad del Agua. https://www.calidaddelagua.org/ 2017. Accessed August 1, 2017.

2. **Sistema de Información Geográfica del Agua (SIGA).** Capas de información de los aprovechamientos del Registro Público de Derechos de Agua (REPDA). http://siga.conagua.gob.mx/REPDA/Menu/FrameKMZ.htm 2015. Accessed August 1, 2017.

3. **Quantum GIS Development Team.** Quantum GIS Geographic Information System. Open Source Geospatial Foundation Project. (Version “Las Palmas” 2.18.0) [computer software]. https://qgis.org 2016. Accessed September 1, 2017.

4. **Instituto Nacional de Estadística y Geografía (INEGI).** Principales resultados por localidad (ITER). https://qgis.org/en/site/ 2017. Accessed August 1, 2017.

5. **World Health Organization (WHO).** Guidelines for Drinking-water Quality. 4th ed. Geneva: WHO; 2011.

6. **Secretaría de Salud (SSA).** Modificación a la Norma Oficial Mexicana NOM-127-SSA11-994, Salud ambiental. Agua para uso y consumo humano. Límites permisibles de calidad y tratamientos a que debe someterse el agua para su potabilización. Mexico: Diario Oficial de la Federación; 2000.

7. **United States Environmental Protection Agency (USEPA).** National Primary Drinking Water Regulations. Washington, DC: Office of Ground Water and Drinking Water, U.S. Environmental Protection Agency. EPA816F02013. Washington, DC: USEPA; 2002.

8. **United States Environmental Protection Agency (USEPA).** National Primary Drinking Water Regulations. Washington, DC: USEPA; 2017.

9. **United States Department of Health and Human Services (USDHHS).** U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries. Public Health Reports. 2015; 130: 11–4.

10. **Secretaría de Salud (SSA).** Norma Oficial Mexicana NOM-201-SSA12-015, Productos y servicios. Agua y hielo para consumo humano, envasados y a granel. Especificaciones sanitarias. Mexico: Diario Oficial de la Federación; 2015.

11. **United States Food and Drug Administration (USFDA).** Guidance for Industry Arsenic in Apple Juice: Action Level. Maryland: FDA; 2013.

12. **Joint FAO and WHO Codex Alimentarius Commission.** Codex Alimentarius Commission. Working document for information and use in discussions related to contaminants and toxins in the GSCTFF Joint FAO and WHO Food Standards Programme. Codex Committee on Contaminants in Foods, Fifth Session. Rome, Italy: FAO and WHO; 2011: 10–12.
13. **Joint FAO and WHO Codex Alimentarius Commission.** Codex Alimentarius Commission: Report of the eighth session of the Codex Committee on Contaminants in Foods Joint FAO/WHO Food Standards Programme. Rome, Italy: FAO and WHO; 2014.

14. **Ministry of Health of the People's Republic of China (MOH).** National Standard of the People's Republic of China: National Food Safety Standard. Maximum Levels of Contaminants in Food. GB 27622-012. Beijing: MOH; 2014.

15. **Commission Regulation (EC).** Commission Regulation (EU) 2015/1006 of 25 June 2015 amending Regulation (EC) No 1881/2006 as regards maximum levels of inorganic arsenic in foodstuffs. *Official Journal of the European Union*. 2015. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:JOL_2015_161_R_0006.

16. **United States Food and Drug Administration (USFDA).** Supporting Document for Action Level for Inorganic Arsenic in Rice Cereals for Infants. Maryland: FDA; 2016.

17. **Joint FAO/WHO Codex Alimentarius Commission.** Codex Alimentarius: Standard for infant formula and formulas for special medical purposes intended for infants. 721–981. Rome, Italy: FAO/WHO; 2007: 1–21.

18. **United States Food and Drug Administration (USFDA).** Anticaries Active Ingredients. Maryland: FDA; 1996.

19. **Secretaria de Salud (SSA).** Modificación de los numerales 2, 3, 6, 8, 9 y 11 de la Norma Oficial Mexicana NOM-040-SSA11-993, Productos y servicios. Sal yodada y sal yodada fluorada. Especificaciones sanitarias. Mexico: Diario Oficial de la Federación; 2010.

20. **Secretaria de Medio Ambiente y Recursos Naturales (SEMARNAT).** Norma Oficial Mexicana NOM-147-SEMARNAT/SSA12-004, Que establece criterios para determinar las concentraciones de remediación de suelos contaminados por arsénico, bario, berilio, cadmio, cromo hexavalente, mercurio, níquel, plata, plomo, selenio, talio y/o vanadio. Vol 2017. Mexico Diario Oficial de la Federación; 2004.

21. **United Kingdom Environment Agency (UKEA).** Soil Guidance Values for Inorganic Arsenic in Soil. Science Report SC050021/arsenic SGV. Rotherdam: UKEA; 2009.

22. **Canadian Council of Ministers of the Environment (CCME).** Canadian Soil Quality Guidelines for the Protection of Environmental and Human Health. September 2007.

23. **Sariñana-Ruiz YA, Vazquez-Arenas J, Sosa-Rodríguez FS.** Assessment of arsenic and fluorine in surface soil to determine environmental and health risk factors in the Comarca Lagunera, Mexico. *Chemosphere*. 2017; 178: 391–401. DOI: https://doi.org/10.1016/j.chemosphere.2017.03.032

24. **Agency for Toxic Substances and Disease Registry (ATSDR).** Toxicological Profile for Arsenic. Atlanta: ATSDR; 2017.

25. **Calderon J, Navarro ME, Jimenez-Capdeville ME, et al.** Exposure to arsenic and lead and neuropsychological development in Mexican children. *Environ Res*. 2001; 85: 69–76. DOI: https://doi.org/10.1006/ensr.2000.4106

26. **Rosado JL, Ronquillo D, Kordas K, et al.** Arsenic exposure and cognitive performance in Mexican schoolchildren. *Environ Health Perspect*. 2007; 115: 1371–5. DOI: https://doi.org/10.1289/ehp.9961

27. **Roy A, Kordas K, Lopez P, et al.** Association between arsenic exposure and behavior among first-graders from Torreon, Mexico. *Environ Res*. 2011; 111: 670–6. DOI: https://doi.org/10.1016/j.envres.2011.03.003

28. **Rocha-Amador D, Navarro ME, Carrizales L, Morales R, and Calderon J.** Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. *Cad Saude Publica*. 2007; 23 (Suppl4): S579–87. DOI: https://doi.org/10.1590/S0102-311X2007001600018

29. **Soto-Pena GA, Luna AL, Acosta-Saaedra L, et al.** Assessment of lymphocyte subpopulations and cytokine secretion in children exposed to arsenic. *FASEB J*. 2006; 20: 779–81. DOI: https://doi.org/10.1096/fj.05-4860fje

30. **Pineda-Zavaleta AP, Garcia-Vargas G, Borja-Aburto VH, et al.** Nitric oxide and superoxide anion production in monocytes from children exposed to arsenic. *Toxicol Appl Pharmacol*. 2003; 198: 283–90. DOI: https://doi.org/10.1016/S0041-008X(03)00034-9

31. **Olivas-Calderon E, Recio-Vega R, Gandolfi AJ, et al.** Lung inflammation biomarkers and lung function in children chronically exposed to arsenic. *Toxicol Appl Pharmacol*. 2015; 287: 161–7. DOI: https://doi.org/10.1016/j.taap.2015.06.001

32. **Recio-Vega R, Gonzalez-Cortes T, Olivas-Calderon E, Lantz RC, Gandolfi AJ, and Gonzalez-De Alba C.** In utero and early childhood exposure to arsenic decreases lung function in children. *J Appl Toxicol*. 2015; 35: 358–66. DOI: https://doi.org/10.1002/jat.3023

33. **Gamiño-Gutierrez SP, Gonzalez-Perez CI, Gonsebatt ME, and Monroy-Fernandez MG.** Arsenic and lead contamination in urban soils of Villa de la Paz (Mexico) affected by historical mine wastes and its effect on children’s health studied by micronucleated exfoliated cells assay. *Environ Geochem Health*. 2013; 35: 37–51. DOI: https://doi.org/10.1007/s10653-012-9469-8

34. **Jasso-Pineda Y, Diaz-Barriga F, Calderon J, Yanez L, Carrizales L, and Perez-Maldonado IN.** DNA damage and decreased DNA repair in peripheral blood mononuclear cells in individuals exposed to arsenic and lead in a mining site. *Biol Trace Elem Res.*
2012; 146: 141–9. DOI: https://doi.org/10.1007/s12011-011-9237-0

35. Sampaio-Reyes A, Hernandez A, El-Yamani N, et al. Arsenic induces DNA damage in environmentally exposed Mexican children and adults. Influence of GSTO1 and AS3MT polymorphisms. Toxicol Sci. 2010; 117: 63–71. DOI: https://doi.org/10.1093/toxsci/kfq173

36. González-Cortes T, Recio-Vega R, Lantz RC and Chau BT. DNA methylation of extracellular matrix remodeling genes in children exposed to arsenic. Toxicol Appl Pharmacol. 2017; 329: 140–47. DOI: https://doi.org/10.1016/j.taap.2017.06.001

37. Laine JE, Bailey KA, Rubio-Andrade M, et al. Maternal arsenic exposure, arsenic methylation efficiency, and birth outcomes in the Biomarkers of Exposure to ARsenic (BEAR) pregnancy cohort in Mexico. Environ Health Perspect. 2015; 123: 186–92.

38. Rager JE, Bailey KA, Smeester L, et al. Prenatal arsenic exposure and the epigenome: altered microRNAs associated with innate and adaptive immune signaling in newborn cord blood. Environ Mol Mutagen. 2014; 55: 196–208. DOI: https://doi.org/10.1002/em.21842

39. Perez-Vazquez MS, Ochoa-Martinez AC, Rulz-Vera T, Araiza-Gamboa Y and Perez-Maldonado IN. Evaluation of epigenetic alterations (mir-126 and mir-155 expression levels) in Mexican children exposed to inorganic arsenic via drinking water. Environ Sci Pollut Res Int. 2017; 24(36): 28036–28045. DOI: https://doi.org/10.1007/s11356-017-0367-6

40. Alegría-Torres JA, Carrizales-Yanez L, Díaz-Barriga F, et al. DNA methylation changes in Mexican children exposed to arsenic from two historic mining areas in San Luis Potosí. Environ Mol Mutagen. 2016; 57: 717–23. DOI: https://doi.org/10.1002/em.22062

41. Osorio-Yáñez C, Ayllon-Vergara JC, Aguilar-Madrid G, et al. Carotid intima-media thickness and plasma asymmetric dimethylarginine in Mexican children exposed to inorganic arsenic. Environ Health Perspect. 2013; 121: 1090–6.

42. Osorio-Yáñez C, Ayllon-Vergara JC, Arreola-Mendoza L, et al. Blood pressure, left ventricular geometry, and systolic function in children exposed to inorganic arsenic. Environ Health Perspect. 2015; 123: 629–35.

43. Cárdenas-González M, Osorio-Yáñez C, Gaspar-Ramírez O, et al. Environmental exposure to arsenic and chromium in children is associated with kidney injury molecule-1. Environ Res. 2016; 150: 653–62. DOI: https://doi.org/10.1016/j.envres.2016.06.032

44. National Research Council (NRC). Fluoride in Drinking Water: A Scientific Review of EPA’s Standards. Washington, DC: The National Academies Press; 2006.

45. Hernández-Martínez CT, Medina-Solís CE, Robles-Bermeo NL, et al. Oral hygiene customs in 61–2 year old schoolchildren. Rev Invest Clin. 2014; 66: 157–63.

46. Hernández-Guerrero JC, de la Fuente HJ, Ledesma-Montes C, Fontana-Uribe B and Jiménez-Farfán D. Fluoride concentration in toothpastes of the Mexican market. Bol Méd Hosp Infantil Mex. 2005; 62: 19–24.

47. Secretaria de Salud (SSA). Aviso de Cancelación del Proyecto de Norma Oficial Mexicana PROY-219-SSA12-002, Límites máximos de concentración de fluoruros en productos higiénico-odontológicos e insumos de uso odontológicos fluorados. Mexico: Diario Oficial de la Federación; 2011.

48. De la Cruz Cardoso D, Tapia Sandovál S, Sánchez Barrón C and Pinelo Bolaños P. Fluoride intake from toothpaste use in preschoolers. Revista Odonto Ciencia; 2010.

49. Molina-Frechero N, Durán-Merino D, Castañeda-Castanera E, Juárez-López MLA. La caries y su relación con la higiene oral en preescolares mexicanos. Gac Méd Mex. 2015; 151: 485–90. https://www.anmm.org.mx/GMM/2015/n4/GMM_151_2015_4_4854–90.pdf

50. Maguire A, Zohouri FV, Hindmarch PN, Hats J and Moynihan PJ. Fluoride intake and urinary excretion in 6- to 7-year-old children living in optimally, sub-optimally and non-fluoridated areas. Comm Dent Oral Epid. 2007; 35: 479–88. DOI: https://doi.org/10.1111/j.1600-0528.2006.00366.x

51. Peckham S and Awofeso N. Water fluoridation: a critical review of the physiological effects of ingested fluoride as a public health intervention. Scientific World J. 2014; 2014: 293019. DOI: https://doi.org/10.1155/2014/293019

52. García-Perez A, Igigoyen-Camacho ME and Borges-Yanez A. Fluorosis and dental caries in Mexican schoolchildren residing in areas with different water fluoride concentrations and receiving fluoridated salt. Caries Res. 2013; 47: 299–308. DOI: https://doi.org/10.11159/000346616

53. Barquera S, Campirano F, Bonvecchio A, Hernandez-Barrera L, Rivera JA and Popkin BM. Caloric beverage consumption patterns in Mexican children. Nutr J. 2010; 9: 47. DOI: https://doi.org/10.1186/1475-2891-9-47

54. Loyola-Rodriguez JP, Pozos-Guillén AJ and Hernández-Guerrero JC. Bottled drinks as additional source of fluoride exposure. Salud Publica Mex. 1998; 40: 438–31. DOI: https://doi.org/10.1590/S0036-36341998000500008

55. Denbesten P and Li W. Chronic fluoride toxicity: dental fluorosis. Monogr Oral Sci. 2011; 22: 81–96. DOI: https://doi.org/10.1159/000327028

56. Soto-Rojas AE, Urena-Cirett JL and Martinez-Mier EA. A review of the prevalence of dental fluorosis in Mexico. Rev Panam Salud Pub. 2004; 15: 9–18. DOI: https://doi.org/10.1590/S1020-49892004000100003

57. Aguilar-Díaz FDC, Morales-Corona F, Cintra-Viveiro AC and Fuente-Hernandez J. Prevalence of dental fluorosis in Mexico 2005–2015:
a literature review. Salud Publica Mex. 2017; 59: 306–13.
58. Choi AL, Sun G, Zhang Y and Grandjean P. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. Environ Health Perspect. 2012; 120: 1362–8. DOI: https://doi.org/10.1289/ehp.1104912
59. Valdez Jimenez L, Lopez Guzman OD, Cervantes Flores M, et al. In utero exposure to fluoride and cognitive development delay in infants. Neurotoxicology. 2017; 59: 65–70. DOI: https://doi.org/10.1016/j.neuro.2016.12.011
60. Singh N, Verma KG, Verma P, Sidhu GK and Sachdeva S. A comparative study of fluoride ingestion levels, serum thyroid hormone & TSH level derangements, dental fluorosis status among school children from endemic and non-endemic fluorosis areas. SpringerPlus. 2014; 3: 7. DOI: https://doi.org/10.1186/2193-1801-3-7
61. Xiang Q, Chen L, Liang Y, Wu M and Chen B. Fluoride and thyroid function in children in two villages in China. J Toxicol Environ Health Sci. 2009; 1: 054–59.
62. Dharmaratne RW. Fluoride in drinking water and diet: the causative factor of chronic kidney diseases in the North Central Province of Sri Lanka. Environ Health Prev Med. 2015; 20: 237–42. DOI: https://doi.org/10.1007/s12199-015-0464-4
63. Xiong XZ, Liu JH, He WH, et al. Dose-effect relationship between drinking water fluoride levels and damage to liver and kidney functions in children. Environ Res. 2007; 103: 112–16. DOI: https://doi.org/10.1016/j.envres.2006.05.008
64. Liu H, Gao Y, Sun L, Li M, Li B and Sun D. Assessment of relationship on excess fluoride intake from drinking water and carotid atherosclerosis development in adults in fluoride endemic areas, China. International J Hyg Environ Health. 2014; 217: 413–20. DOI: https://doi.org/10.1016/j.ijiheh.2013.08.001
65. Karademir S, Akcam M, Kuybulu AE, Olgar S and Oktem F. Effects of fluoride on QT dispersion, heart rate variability and echocardiographic parameters in children. The Anatolian J Cardiology. 2011; 150–55. DOI: https://doi.org/10.5152/akd.2011.038
66. Tseng CH. A review on environmental factors regulating arsenic methylation in humans. Toxicol Appl Pharmacol. 2009; 235: 338–350. DOI: https://doi.org/10.1016/j.taap.2008.05.012
67. Mizuta N, Mizuta M, Ito F, et al. An outbreak of acute arsenic poisoning caused by arsenic contaminated soy-sauce (shoyu): a clinical report of 220 cases. Bull Yamanuchi Med School. 1956; 4: 131–50. DOI: https://doi.org/10.2169/bnaka.45.867
68. United States Environmental Protection Agency (USEPA). Regional Screening Levels (RSLs) – Generic Tables (June 2017). Washington, DC: USEPA; 2017.
69. United States Environmental Protection Agency (USEPA). Fluoride: Dose-Response Analysis For Non-cancer Effects. 820-R.019. Health and Ecological Criteria Division, Office of Water. Washington, DC: USEPA; 2010.
70. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for fluorides, hydrogen fluoride and fluorine. Atlanta: ATSDR; 2003.
71. Health Canada (HC). Fourth Report on Human Biomonitoring of Environmental Chemicals in Canada. Results of the Canadian Health Measures Survey Cycle 4. 9780-6600-85272-. Ottawa, Ontario: Health Canada; 2017: 232.
72. Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary References I. Fluoride. In: National Academies Press, ed. Washington D.C.: National Academies Press (US); 1997: 288–313.
73. Signes-Pastor AJ, Vioque J, Navarrette-Munoz EM, et al. Concentrations of urinary arsenic species in relation to rice and seafood consumption among children living in Spain. Environ Res. 2017; 159: 69–75. DOI: https://doi.org/10.1016/j.envres.2017.07.046
74. Skroder Loveborn H, Kippler M, Lu Y, et al. Arsenic Metabolism in Children Differs From That in Adults. Toxicol Sci. 2016; 152: 29–39. DOI: https://doi.org/10.1093/toxsci/kfw060
75. Sun G, Xu Y, Li X, Jin Y, Li B and Sun X. Urinary Arsenic Metabolites in Children and Adults Exposed to Arsenic in Drinking Water in Inner Mongolia, China. Environ Health Perspect. 2007; 115: 648–52. DOI: https://doi.org/10.1289/ehp.9271
76. Torres-Sanchez I, Lopez-Carrillo L, Rosado JL, et al. Sex differences in the reduction of arsenic methylation capacity as a function of urinary total and inorganic arsenic in Mexican children. Environ Res. 2016; 151: 38–43. DOI: https://doi.org/10.1016/j.envres.2016.07.020
77. Hays SM, Becker RA, Leung HW, Aylward LL and Pyatt DW. Biomonitoring equivalents: a screening approach for interpreting biomonitoring results from a public health risk perspective. Regul Toxicol Pharmacol. 2007; 47: 96–109. DOI: https://doi.org/10.1016/j.yrtph.2006.08.004
78. Hays SM, Aylward LL, Gagne M, Nong A and Krishnan K. Biomonitoring equivalents for inorganic arsenic. Regul Toxicol Pharmacol. 2010; 58:1–9. DOI: https://doi.org/10.1016/j.yrtph.2010.06.002
79. Schulz C, Wilhelm M, Heudorf U and Kolossa-Gehring M. Update of the reference and HBM values derived by the German Human Biomonitoring Commission. Int J Hyg Environ Health. 2011; 215: 26–35. DOI: https://doi.org/10.1016/j.ijiheh.2011.06.007
80. Bashash M, Thomas D, Hu H, et al. Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6–12 Years of Age in Mexico. Environ Health Perspect. 2017; 125: 097017. DOI: https://doi.org/10.1289/EHP655
81. Buzalaf MA and Whitford GM. Fluoride metabolism. Monogr Oral Sci. 2011; 22: 20–36. DOI: https://doi.org/10.1159/000325107

82. Villa A, Anabalon M, Zohouri V, Maguire A, Franco AM and Rugg-Gunn A. Relationships between fluoride intake, urinary fluoride excretion and fluoride retention in children and adults: an analysis of available data. Caries Res. 2010; 44: 60–8. DOI: https://doi.org/10.1159/000279325

83. Erdal S and Buchanan SN. A quantitative look at fluorosis, fluoride exposure, and intake in children using a health risk assessment approach. Environ Health Perspect. 2005; 113: 111–7. DOI: https://doi.org/10.1289/ehp.7077

84. Aylward LL, Hays SM, Vezina A, Deveau M, St-Amand A and Nong A. Biomonitoring Equivalents for interpretation of urinary fluoride. Regul Toxicol Pharmacol. 2015; 72: 158–67. DOI: https://doi.org/10.1016/j.yrtph.2015.04.005

85. Umweltbundesamt (UBA). Levels of selected substances in blood and urine of children in Germany. German Environmental Survey for toxicants for interpretation of urinary fluoride. Environ Health Perspect. 2005; 113: 111–7. DOI: https://doi.org/10.1289/ehp.7077

86. Kafaei R, Tahmasbi R, Ravanipour M, Dessau-Roßlau: UBA; 2008.

87. Korda K, Queirolo EI, Manay N, et al. Urinary arsenic, cadmium, manganese, nickel, and vanadium levels of schoolchildren in the vicinity of the industrialised area of Asaluyeh, Iran. Environ Sci Pollut Res Int. 2017; 24: 23498–507. DOI: https://doi.org/10.1159/s11356-017-0998-1

88. Arcega-Cabrera F, Faragher LF, Oceguera-Vargas I, et al. Water Consumption as Source of Arsenic, Chromium, and Mercury in Children Living in Rural Yucatan, Mexico: Blood and Urine Levels. Bull Environ Contam Toxicol. 2017.

89. Arcega-Cabrera F and Faragher LF. Education, fish consumption, well water, chicken coops, and cooking fires: Using biogeochemistry and ethnography to study exposure of children from Yucatan, Mexico to metals and arsenic. Sci Total Environ. 2016; 568: 75–82. DOI: https://doi.org/10.1016/j.scitotenv.2016.05.209

90. Kordas K, Queirolo EI, Manay N, et al. Low-level arsenic exposure: Nutritional and dietary predictors in first-grade Uruguayan children. Environ Res. 2016; 147: 16–23. DOI: https://doi.org/10.1016/j.envres.2016.01.022

91. Signes-Pastor AJ, Carey M, Vioque J, et al. Urinary Arsenic Speciation in Children and Pregnant Women from Spain. Expo Health. 2017; 9: 105–11. DOI: https://doi.org/10.1007/s12403-016-0225-7

92. Molina-Villalbal, Lacasana,M, Rodriguez-Barranco M, et al. Biomonitoring of arsenic, cadmium, lead, manganese and mercury in urine and hair of children living near mining and industrial areas. Chemosphere. 2015; 124: 83–91. DOI: https://doi.org/10.1016/j.chemosphere.2014.11.016

93. Davis MA, Mackenzie TA, Cottingham KL, Gilbert-Diamond D, Punshon T and Karagas MR. Rice consumption and urinary arsenic concentrations in U.S. children. Environ Health Perspect. 2012; 120: 1418–24. DOI: https://doi.org/10.1289/ehp.1205014

94. Caldwell KL, Jones RL, Verdon CP, Jarrett JM, Caudill SP and Osterloh JD. Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 20032-004. J Expo Sci Environ Epidemiol. 2009; 19: 59–68. DOI: https://doi.org/10.1038/jes.2008.32

95. Ramsubhag S, Naidu RS, Narinesingh D, Teelucksingh S. Urinary fluoride levels in children in a single school in Trinidad and Tobago: a preliminary investigation. West Indian Med J. 2006; 55: 440–3. DOI: https://doi.org/10.1556/00043-3144200600060014

96. Jimenez-Farfan MD, Hernandez-Guerrero JC, Juarez-Lopez LA, Jacinto-Aleman LF and de la Fuente-Hernandez J. Fluoride consumption and its impact on oral health. Int J Environ Res Public Health. 2011; 8: 148–60. DOI: https://doi.org/10.3390/ijerph8010148

97. Wang C, Gao Y, Wang W, et al. A national cross-sectional study on effects of fluoride-safe water supply on the prevalence of fluorosis in China. BMJ Open. 2012; 2. DOI: https://doi.org/10.1136/bmjopen-2012-001564

98. Zohoori FV and Maguire A. Determining an Upper Reference Value for the Urinary Fluoride-Creatinine Ratio in Healthy Children Younger than 7 Years. Caries Res. 2017; 51: 283–89. DOI: https://doi.org/10.1159/000472263

99. Moreno ME, Acosta-Saaavedra LC, Meza-Figueroa D, et al. Biomonitoring of metal in children living in a mine tailings zone in Southern Mexico: A pilot study. Int J Hyg Environ Health. 2010; 213: 252–8. DOI: https://doi.org/10.1016/j.ijhheh.2010.03.005

100. Luna AI, Acosta-Saaavedra LC, Lopez-Carrillo L, et al. Arsenic alters monocyte superoxide anion and nitric oxide production in environmentally exposed children. Toxicol Appl Pharmacol. 2010; 245: 244–51. DOI: https://doi.org/10.1016/j.taap.2010.03.006

101. Meza-Montenegro MM, Valenzuela-Quintanar AI, Balderas-Cortes JJ, et al. Exposure assessment of organochlorine pesticides, arsenic, and lead in children from the major agricultural areas in Sonora, Mexico. Arch Environ Contam Toxicol. 2013; 64: 519–27. DOI: https://doi.org/10.1007/s00244-012-9846-4

102. Grijalva-Haro MI, Barba-Leyva ME and Laborin-Alvarez A. Fluoride intake and excretion in children of Hermosillo, Sonora, Mexico. Salud Publica Mex. 2001; 43: 127–34.

103. Rocha-Amador DO, Calderon J, Carrizales L, Costilla-Salazar R and Perez-Maldonado I. Apoptosis of peripheral blood mononuclear cells in children exposed to arsenic and fluoride. Environ Toxicol Pharmacol. 2011; 32: 399–405. DOI: https://doi.org/10.1016/j.etap.2011.08.004
104. Estrada-Capetillo BL, Ortiz-Perez MD, Salgado-Bustamante M, et al. Arsenic and fluoride co-exposure affects the expression of apoptotic and inflammatory genes and proteins in mononuclear cells from children. Mutat Res Genet Toxicol Environ Mutagen. 2014; 761: 27–34. DOI: https://doi.org/10.1016/j.mrgentox.2014.01.006

105. Jarquin-Yanez L, de Jesus Mejia-Saavedra J, Molina-Frechero N, et al. Association between urine fluoride and dental fluorosis as a toxicity factor in a rural community in the state of San Luis Potosí. Scientific World Journal. 2015; 2015: 647184. DOI: https://doi.org/10.1155/2015/647184

106. Suwazono Y, Akesson A, Alfen T, Jarup L and Vahter M. Creatinine versus specific gravity-adjusted urinary cadmium concentrations. Biomarkers. 2005; 10: 117–26. DOI: https://doi.org/10.1080/1354750500159001

107. Schulz C, Angerer J, Ewers U, Heudorf U and Wilhelm M. Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German environmental survey on children 2003-006 (GerES IV). Int J Hyg Environ Health. 2009; 212: 637–47. DOI: https://doi.org/10.1016/j.ijeh.2009.05.003

108. National Research Council (NRC). Critical Aspects of EPA’s IRIS Assessment of Inorganic Arsenic: Interim Report. Washington, DC: The National Academies Press; 2013.

109. Camps J and Garcia-Heredia A. Introduction: oxidation and inflammation, a molecular link between non-communicable diseases. Adv Exp Med Biol. 2014; 824: 1–4. DOI: https://doi.org/10.1007/978-3-319-07320-0_1

110. Prüss-Ustün A, Wolf J, Corvalán C, Bos R and Neira M. Preventing disease through healthy environments: A global assessment of the burden of disease from environmental risks. Geneva. http://apps.who.int/iris/bitstream/10665/204585/1/9789241565196_eng.pdf?ua=1. Accessed 2016.

111. Srivastava RK and Bachani D.Burden of NCDs, Policies and Programme for Prevention and Control of NCDs in India. Indian J Community Med. 2011; 36: S7–S12. DOI: https://doi.org/10.4103/0970-0218.94703

112. Yunus M, Sohel N, Hore SK and Rahman M. Arsenic exposure and adverse health effects: A review of recent findings from arsenic and health studies in Matlab, Bangladesh. The Kaohsiung J of Medical Sciences. 2011; 27: 371–76. DOI: https://doi.org/10.1016/j.kjms.2011.05.012

113. Abegunde DO, Mathers CD, Adam T, Ortegon M and Strong K. The burden and costs of chronic diseases in low-income and middle-income countries. Lancet. 2007; 370: 1929–38. DOI: https://doi.org/10.1016/S0140-6736(07)61696-1

114. Nigra AE, Sanchez TR, Nachman KE, et al. The effect of the Environmental Protection Agency maximum contaminant level on arsenic exposure in the USA from 2003 to 2014: an analysis of the National Health and Nutrition Examination Survey (NHANES). The Lancet Public Health. 2017; 2: e513–e21. DOI: https://doi.org/10.1016/S2468-2667(17)30195-0

115. Ko L and Thiessen KM. A critique of recent economic evaluations of community water fluoridation. Int J Occup Environ Health. 2015; 21: 91–120. DOI: https://doi.org/10.1179/2049396714Y.00000000093

116. Fewtrell L, Fuge R and Kay D. An estimation of the global burden of disease due to skin lesions caused by arsenic in drinking water. J Water Health. 2005; 3: 101–7. DOI: https://doi.org/10.2166/wh.2005.0011

117. Oberoi S, Barchowsky A and Wu F. The global burden of disease for skin, lung, and bladder cancer caused by arsenic in food. Cancer Epidemiol Biomarkers Prev. 2014; 23: 1187–94. DOI: https://doi.org/10.1158/1055-9965.EPI-13-1317

118. Fewtrell L, Smith S, Kay D and Bartram J. An attempt to estimate the global burden of disease due to fluoride in drinking water. J Water Health. 2006; 4: 533–42. DOI: https://doi.org/10.2166/wh.2006.0036

119. Ochoa-Martinez AC, Orta-Garcia ST, Rico-Escobar EM, et al. Exposure Assessment to Environmental Chemicals in Children from Ciudad Juarez, Chihuahua, Mexico. Arch Environ Cont Toxicol. 2016; 70: 657–670. DOI: https://doi.org/10.1007/s00244-016-0273-9

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