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Biomonitoring Equivalents for interpretation of urinary fluoride

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ABSTRACT

Exposure to fluoride is widespread due to its natural occurrence in the environment and addition to drinking water and dental products for the prevention of dental caries. The potential health risks of excess fluoride exposure include aesthetically unacceptable dental fluorosis (tooth mottling) and increased skeletal fragility. Numerous organizations have conducted risk assessments and set guidance values to represent maximum recommended exposure levels as well as recommended adequate intake levels based on potential public health benefits of fluoride exposure. Biomonitoring Equivalents (BEs) are estimates of the average biomarker concentrations corresponding to such exposure guidance values. The literature on daily urinary fluoride excretion rates as a function of daily fluoride exposure was reviewed and BE values corresponding to the available US and Canadian exposure guidance values were derived for fluoride in urine. The derived BE values range from 1.1 to 2.1 mg/L (1.2–2.5 μg/g creatinine). Concentrations of fluoride in single urinary spot samples from individuals, even under exposure conditions consistent with the exposure guidance values, may vary from the predicted average concentrations by several-fold due to within- and across-individual variation in urinary flow and creatinine excretion rates and due to the rapid elimination kinetics of fluoride. Thus, the BE values are most appropriately applied to screen population central tendency estimates for biomarker concentrations rather than interpretation of individual spot sample concentrations.

1. Introduction

Fluoride is naturally occurring in food, water, soil and air, and can also be added to drinking water, dental products such as toothpaste and mouthwash, and in supplements for the prevention of dental caries. Thus, exposure is widespread. The public health benefits associated with the use of fluorides in dental products and in drinking water have been established, but undesirable outcomes associated with elevated exposures to fluoride are also recognized (Health Canada, 2010). The undesirable outcomes include cosmetic effects (mottling of teeth) associated with excess fluoride, and, at higher levels, adverse effects on skeletal integrity. Tolerable exposure levels are established to protect against potential adverse effects while optimal levels focus on optimizing dental health benefits while remaining well below tolerable exposure levels. Total intakes from drinking water, food, dentifrice, air and soil are considered to estimate the proportion of fluoride allocated to each source of exposure. Drinking water concentration standards and guidelines are targeted so that total fluoride intake from all sources does not exceed exposure guidance values such as tolerable daily intakes (TDIs) or reference doses (RfDs) (Health Canada, 2010; USEPA, 2010).

Fluoride in urine has also been widely used as a biomarker of exposure (Rugg-Gunn et al., 2011; Villa et al., 2010). Measured concentrations of fluoride in urine cannot be directly interpreted in terms of the available exposure guidance values. The purpose of this evaluation is to derive Biomonitoring Equivalent (BE) values for interpretation of population urinary fluoride concentrations. BE values are estimates of the concentration of a chemical or its metabolite in blood or urine that are consistent with risk assessment-derived exposure guidance values such as RfDs or TDIs (Hays et al., 2007, 2008; Angerer et al., 2011). BE values can be used as screening values for the assessment of biomonitoring data in order to provide an initial evaluation of whether the detected concentrations are below, near, or above the concentrations consistent with current exposure guidance values (for both toxicity and nutritional requirements). This evaluation is directed at fluoride anion in urine, which arises from exposure to fluoride from all sources including drinking water, dentifrices, supplements, food, air and soil.

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Concerns regarding potential adverse effects of exposure to fluoride focus on two main outcomes: moderate dental fluorosis with widespread mottling of tooth enamel, which is considered to be an adverse effect due to cosmetic impacts when it reaches a moderate level (Health Canada, 2010; EPA, 2010), and skeletal fluorosis at elevated fluoride exposure levels over a long period of time (Health Canada, 2010). These effects have been observed in several studies of human populations with well-characterized levels of fluoride intake, allowing for robust derivation of no-observed-adverse-effect-levels and lowest-observed-adverse-effect levels (NOAELs and LOAELs). Fluoride has also been considered to be beneficial to public health because of its ability to protect against the development of caries (IOM, 1997).

We derive here BE values that can be used as benchmarks to evaluate measured urinary fluoride concentrations. The fluoride BE values are derived using average age-specific values for urinary parameters such as urine flow rate and creatinine excretion rates, as well as an assumption of steady-state exposure. We also include an evaluation of the variation in urinary fluoride concentrations expected to be observed, due to within- and across-individual variation in urinary spot sample flow and creatinine excretion rates, as well as to temporal variations associated with the rapid excretion of fluoride in urine.

2. Materials and methods

The approach used for the derivation of the urinary BE value for fluoride follows the same general approach used for many other urinary analytes, the urinary mass balance approach. Specifically, the BE value associated with the following exposure guidance values: Health Canada tolerable daily intake (TDI), the ATSDR minimal risk level (MRL), the US EPA reference dose (RfD), and the tolerable upper intake levels (ULs) and adequate intakes (AIs) by the US Institute of Medicine (IOM) can be calculated using data from studies of human populations that relate urinary excretion of fluoride under steady-state exposure conditions to daily intake of fluoride. The estimated daily urinary fluoride excretion rate (DUFE, mg/kg-d) corresponding to an exposure guidance value such as the TDI, is then divided by the estimated body weight-adjusted daily urinary volume (V_{24}, ml/kg-d) or creatinine excretion (CE_{24}, mg/kg-d) to calculate the corresponding BE value (mg/L or mg/g creatinine):

$$BE = \frac{DUFE_{TDI}}{V_{24} \text{ or } CE_{24}} \quad (1)$$

These calculations are conducted for a variety of age ranges using age-specific parameterizations for DUFE, V_{24}, and CE_{24}. To the extent that values differ among age groups, age-specific BE values are reported.

Data and parameters required for this approach include health-based exposure guidance values such as a tolerable daily intake, data allowing for estimation of urinary excretion of fluoride as a function of intake under steady-state conditions, and age-specific and bodyweight-adjusted values for daily urinary flow or creatinine excretion.

We reviewed the available literature and government documents to identify exposure guidance values for fluoride from the United States and Canada. We also obtained and reviewed literature on the pharmacokinetics of fluoride in humans, with a focus on studies that examine the urinary mass balance of fluoride in the range of exposure levels likely to be encountered in the general population in the US and Canada.

We used recent data from the US National Health and Nutrition Examination Survey (NHANES), as well as data obtained from the literature, to characterize body weight-adjusted urinary flow rates and daily creatinine excretion rates as a function of age. Data on urinary flow rates and creatinine excretion rates from the NHANES 2009–2010 survey cycle was downloaded and descriptive statistics were generated using STATA IC 9 (Stata Corp, College Station, TX).

3. Results

3.1. Exposure guidance values

The health effects of excessive exposure to fluoride have been studied extensively, and exposure guidance values have been established by many organizations, including Health Canada (Health Canada, 2010), the US Environmental Protection Agency (USEPA, 2010), the US Agency for Toxic Substances and Disease Registry (ATSDR, 2003), and the US IOM (1997) (Table 1). The risk

Table 1
Available exposure guidance values for fluoride.

Organization, criteria (year of evaluation)	Study description	Critical endpoint and dose	Uncertainty factors	Value
Exposure guidance values based on adverse health effects				
Health Canada, chronic oral TDI (2010)	Studies of the occurrence of dental fluorosis	NOAEL for moderate dental fluorosis, accounting for multi-route exposures, 0.105 mg/kg-d	1	0.105 mg/kg-d
EPA, chronic oral RfD (2010)	Studies of tooth mottling in children at varying fluoride concentrations in water	NOAEL for objectionable dental fluorosis, a cosmetic effect, 0.08 mg/kg-d	1	0.08 mg/kg-d
ATSDR, chronic oral MRL (2003)	Study of risk of bone fractures in elderly persons in China exposed to fluoride in drinking water	NOAEL for increased risk of bone fractures, 0.15 mg/kg-d	3	0.05 mg/kg-d
IOM, UL, infant to age 8 (1997)	Multiple studies on occurrence of moderate dental fluorosis	LOAEL for moderate, cosmetically objectionable dental fluorosis (see Table 2), 0.1 mg/kg-d	1	0.1 mg/kg-d (ages infant to 8)
IOM, UL, ages ⩾ 8 (1997)	Multiple studies of the occurrence of skeletal fluorosis	NOAEL for development of early signs of skeletal fluorosis, 10 mg/d	1	10 mg/d (ages ⩾ 8)
Exposure guidance values based on health benefits				
IOM, AI, age ⩽ 6 months (1997)	Studies indicating no increased risk of dental caries in infants fed human milk ⩽ 6 months	Average dietary fluoride intake in human milk-fed infants, 0.01 mg/d	1	0.01 mg/d (0.001 to 0.003 mg/kg-d)
IOM, AI, age > 6 months (1997)	Studies of intake in communities with water concentrations previously identified to be optimally fluoridated for protective effect against dental caries	Average dietary fluoride intake in infants and children from fluoridated communities, to provide protection against dental caries without unwanted health effects 0.05 mg/kg-d	1	0.05 mg/kg-d

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