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Cadmium exposure and tobacco consumption: Biomarkers and risk assessment

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ABSTRACT

To investigate whether cadmium has an independent role in diseases associated with tobacco consumption, epidemiology data were reviewed, biomonitoring data were analyzed, and probabilistic risk assessment (PRA) was performed. Results from previous epidemiology studies have indicated that there are adverse health effects potentially in common between cadmium exposure and tobacco consumption. Analysis of publically available biomonitoring data showed that blood (B–Cd) and urine (U–Cd) cadmium were higher in cigarette smokers compared with smokeless tobacco (SLT) consumers, and B–Cd and U–Cd in SLT consumers were not significantly different than in non-consumers of tobacco. Comparison with previously established biomonitoring equivalent (BE) values indicated that B–Cd and U–Cd in the majority of these cigarette smokers and SLT consumers did not exceed the blood and urine BEs. Results of the PRA showed that the mean hazard estimate was below a generally accepted regulatory threshold for SLT consumers, but not for cigarette smokers. In total, this evaluation indicated that cadmium exposures in tobacco consumers differed by product category consumed; cadmium in tobacco may not be associated with tobacco consumption related diseases; if cadmium in tobacco contributes to tobacco consumption related diseases, differences in hazard and/or risk may exist by product category.

1. Introduction

Soil cadmium concentrations vary throughout the tobacco growing regions of the world. Major sources of soil cadmium contamination include natural environmental processes (e.g., volcanic activity) (WHO, 1992a,b), emissions from the nonferrous metals industry (Nriagu and Pacyna, 1988), and agricultural application of sewage sludge and phosphate fertilizers (WHO, 1992a,b). The tobacco plant can accumulate cadmium, with uptake into the roots and leaves primarily influenced by tobacco species and soil characteristics (Järup and Akesson, 2009; Wagner and Yeargan, 1986; Westcott and Spincer, 1974; WHO, 1992a,b). Accordingly, cadmium is measurable in tobacco and in cigarette mainstream smoke (MSS). Cadmium concentration in both non-combusted and combusted tobacco products varies with global sources of tobacco, and cadmium concentration in cigarette MSS may also vary with cigarette physical design parameters such as ventilation and filtration (Bache et al., 1987; Figueres and de Salles de Hys, 1994; Kalaitzoglou and Samara, 1999; Perinelli and Carugno, 1978). In certain smokeless tobacco (SLT) products, cadmium concentrations have been reported to range between 450 and 1,880 ng per gram dry weight (Hoffmann et al., 1987; Maier et al., 1989; Pappas et al., 2008). In non-combusted cigarette tobacco, cadmium has been reported at concentrations between 100 and 4,950 ng per gram of tobacco (Viana et al., 2011; Westcott and Spincer, 1974; Yue, 1992). And in cigarette MSS, depending on cigarette design and the machine smoking regimen, cadmium concentrations between 1.6 and 222 ng per cigarette have been reported (Counts et al., 2005; IARC, 2004). MSS cadmium levels in counterfeit cigarettes have been reported to be 2–7 times higher than authentic cigarette brands (Pappas et al., 2007). Actual human exposure to cadmium from consumption of tobacco products may vary with product category (i.e., combustible vs. non-combustible products), as well as with duration, intensity, and frequency of product consumption.

Biomarkers of cadmium exposure, including blood and urine cadmium (B–Cd and U–Cd, respectively) are established. Typically, B–Cd is considered related to recent cadmium exposure (Hays et al., 2008a; Järup and Akesson, 2009). U–Cd is considered to be a relevant marker of chronic cadmium exposure as well as renal concentrations of cadmium. The kidney is deemed the critical organ for cadmium toxicity in humans. A widely accepted indicator of kidney damage is the increased excretion of low molecular weight proteins (i.e., proteinuria) (Järup and Akesson, 2009), indicating kidney effects preceding kidney damage. The concentration of cadmium in the cortex of the kidney has been identified as the dose metric most often associated with cadmium-induced proteinuria (Hays et al., 2008a), and thus cadmium non-cancer risk assessments rely on estimates of internal dose (i.e., U–Cd or renal cortex cadmium concentration) from human populations for the

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determination of acceptable cadmium exposure levels. As U–Cd concentrations are most closely associated with the concentration of cadmium in the renal cortex, U–Cd concentration is useful as a surrogate for the dose metric associated with the critical toxic response. Cadmium exposure is also associated with bone and respiratory damage in humans and is considered a known (IARC, 1993) or probable (USEPA, 1992) human carcinogen, with the lung as the specified target organ. U–Cd was associated with cancer mortality in men and women in a recently published study in the United States (US) (Adams et al., 2012). Other systems possibly affected by cadmium exposure are cardiovascular, immunological, hematopoietic, and hepatic (Järup and Akesson, 2009; Fowler, 2009). As noted, however, the kidney is identified as the most sensitive target in humans, and for risk assessment, most non-cancer exposure guidance values for cadmium are based on protection against cadmium-induced kidney damage.

Despite the chemical and physical complexity of cigarette MSS and the inter-and intra-variability in human cigarette smoking behavior, it has been suggested that it may be possible to reduce cigarette MSS toxicity by reduction of constituents most likely to be associated with cigarette smoking-related disease. For example, the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) has included cadmium on the list of cigarette MSS constituents of "high priority for disclosure and monitoring of their levels by brand", although cadmium is not currently recommended by the FCTC for mandatory lowering (Burns et al., 2008). Additionally, an analysis by Cox (2006) concluded, based on potential mechanisms of cadmium carcinogenicity, that removing cadmium from cigarette MSS may result in a significantly decreased risk of smoking-related lung cancer. Draft guidance issued by the US Food and Drug Administration identified cadmium on the abbreviated list of harmful and potentially harmful constituents in roll-your-own tobacco and cigarette filler as well as SLT (USDHHS, 2012).

In an attempt to investigate if cadmium is independently associated with tobacco consumption related adverse health outcomes in tobacco consumers, this study estimated and compared U–Cd and B–Cd in cigarette smokers, SLT consumers, and non-consumers of tobacco using publically available survey data representative of the US population. Estimated U–Cd and B–Cd values were then compared with (1). biological cadmium concentrations associated with adverse health outcomes from previously published epidemiological studies and (2). established biomonitoring equivalent (BE) values for blood and urine (Hays et al., 2008a). A BE is "the concentration or range of concentrations of chemical in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guideline." (Hays et al., 2008a.) It has been suggested that the derivation and use of BEs may be useful for the interpretation of human biomonitoring data in the context of public health risk assessment (Hays et al., 2008a).

In addition, a probabilistic risk assessment (PRA), including incremental lifetime cancer risk (ILCR) and hazard quotient (HQ) calculations specific to cadmium exposures from cigarette smoking and SLT consumption, was performed. PRA is a scientific evidence based tool that can be used to estimate non-cancer hazard and cancer risk. In the application conducted and presented here, PRA incorporated the range of potential exposures to cadmium, as well as the range of human characteristics related to exposure to tobacco products. To varying degrees, similar methodologies have been used to estimate non-cancer hazards and cancer risks of chemicals in occupational and environmental settings (e.g., OSHA, 1992), as well as in cigarette MSS and SLT products (e.g., Arias, 2006; Fowles and Dybing, 2003).

With these tools, cadmium exposure from cigarette smoking and SLT consumption, as well as the potential association between cadmium exposure and tobacco consumption related diseases, was evaluated.

2. Methods

2.1. Determination of relevant human health endpoints

Publicly available documents from scientific and public health groups were reviewed to identify generally accepted adverse human health effects associated with both cadmium exposure and tobacco consumption (both cigarette smoking and SLT consumption). For well-defined adverse effects, biologically relevant (i.e., blood or urine) cadmium concentrations associated with these endpoints were identified. The lowest value associated with a relevant effect was obtained. For cadmium, the Agency for Toxicological Substances and Disease Registry (ATSDR, 2008) toxicological profile was reviewed followed by review of relevant primary peer-reviewed publications. ATSDR is a US federal public health agency that provides summaries of toxicological data for certain hazardous substances via peer-reviewed toxicological profiles. For health outcomes causally associated with cigarette smoking, the US Surgeon General 2004 report (USDHHS, 2004) was reviewed. For the identification of health endpoints associated with SLT consumption, conclusions from the following scientific consensus groups were consulted: International Agency for Research on Cancer (IARC, 2007), Life Sciences Research Organization (LSRO, 2008), Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR, 2008), and the US Surgeon General (USDHHS, 1986). Additionally, a literature search was conducted in order to identify potentially relevant primary studies published more recently.

2.2. Biomonitoring data

Data collected in the National Health and Nutrition Examination Survey (NHANES) Mobile Examination Centers (MEC) from 1999 to 2006 for individuals aged 20 years and older were used to evaluate B–Cd and U–Cd in cigarette smokers, SLT consumers, and non-consumers of tobacco. NHANES is conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) and is designed to annually assess the health and nutritional status of adults and children in the US. Data are publicly available for download and analysis and are representative of the civilian, non-institutionalized US population. Detailed survey methodology is available (CDC, 2006).

In this analysis, the categories for tobacco consumption (snuff, chewing tobacco, or cigarettes) or non-consumption were determined by an individual indicating on the NHANES MEC questionnaire that a particular tobacco product (category) was consumed (or not consumed) in the last 5 days. Self-reported snuff (from the questionnaire: "such as Skoal, Skoal Bandits, or Copenhagen") and chewing tobacco (from the questionnaire: "such as Redman, Levi Garrett, or Beechnut") consumers were combined into one SLT category due to sample size limitations. Only exclusive tobacco consumers were included (i.e., individuals reporting the consumption of multiple tobacco products or pipes, cigars, or nicotine replacement therapy were excluded). Self-reported non-consumers with a serum cotinine value greater than 15 ng per mL (NCI, 1999) were excluded from the analysis. Individuals were also excluded if data regarding tobacco consumption were missing or if a response was refused or reported as "do not know". B–Cd was measured in all participants in all survey periods; U–Cd was measured in a randomly selected one-third subset of the population (CDC, 2009).

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Multiple linear regression models for the natural log transformed B–Cd and U–Cd data were constructed and included adjustment for age (six categories: 20–29, 30–39, 40–49, 50–59, 60–69, ⩾70 years), gender (two categories: male, female), race/ethnicity (four categories: non-Hispanic Black, non-Hispanic White, Hispanic, Other), body mass index (four categories: ⩽22.7, 22.8–26.1, 26.2–30.2, ⩾30.3), urinary creatinine, survey year (four categories: 1999–2000, 2001–2002, 2003–2004, 2005–2006), and tobacco consumption category. All analyses were performed using the appropriate statistical weights and design parameters as prescribed by NCHS. The survey procedures available in SAS v.9.1 (SAS Institute Inc., Cary, NC) and the survey package available for R v.2.9.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for the analyses (Lumley, 2010). The data were log-transformed to better meet the assumptions for modeling (i.e., normality).

2.3. Biomonitoring equivalents (BEs)

Comparison of biological levels of cadmium measured in tobacco consumers with established BE values may be useful for understanding differential exposure and therefore differential potential for disease risk in the different consumption groups. Guidelines for the development or derivation of BE have been described previously (Hays et al., 2008b). Cadmium BEs for urine and blood have been established based on US Environmental Protection Agency (EPA) reference dose (RfD) point of departure values for which the human kidney is the target organ (Hays et al., 2008a). Using U–Cd and B–Cd values for cigarette smokers and SLT consumers in NHANES 1999–2006 (as described in Section 2.2 above), the percentages of cigarette smokers and SLT consumers above established BEs of 1.5 μg/L urine and 1.7 μg/L blood (Hays et al., 2008a) were tabulated using the appropriate statistical weights and design parameters as prescribed by the NCHS.

2.4. Cadmium concentrations in cigarette MSS

Cadmium concentrations in tobacco were determined for input into the PRA model. Thirty-four cigarette brands representative of the 2005–2006 US cigarette market were selected for analysis. Seven brands were in the 'tar' category of 1 to 6 mg per cigarette, seventeen brands were in the 'tar' category of 9 to 12 mg per cigarette, and ten brands were in the 'tar' category of 13 to 19 mg per cigarette, with 'tar' category determined by the Cambridge Filter Method (previously known as the Federal Trade Commission method, where a 35 cc puff is taken every 60 s for a 2 s duration with no cigarette ventilation holes blocked) (FTC, 1967; Pillsbury et al., 1969). Cigarettes were purchased in the US in 2006 and data were collected under an intense machine-smoking regimen, i.e., 60 cc puff, twice every minute, for a 2 s duration with 50% blocking of filter ventilation. Cigarettes were conditioned and machine-smoked at 60% relative humidity at 75 °F to a butt length of tipping plus 3 mm according to the Federal Trade Commission method (FTC, 1967; Pillsbury et al., 1969). Smoke condensate was collected by electrostatic precipitation using a 20 port rotary smoking machine. The samples were extracted with methanol and concentrated under nitrogen followed by closed vessel digestion with nitric acid in a microwave digestion system. For determination of cadmium content, the resulting solutions were analyzed in triplicate using the Health Canada method T-109, (Canada, 1999), with the following exceptions: only nitric acid was used in the sample digestion and inductively coupled mass spectrometry was used as the detector system.

2.5. Cadmium concentrations in SLT products

As part of a survey of the chemical composition of SLT products sold in the US in 2006 and 2007, cadmium concentrations were determined in twenty-three moist snuff and seven chewing tobacco products. Products were purchased in March–April of 2006 or April–June 2007. Determination of cadmium content was according to Health Canada method T-306 (Canada, 2000) and analyses were conducted by Labstat International ULC (Kitchener, Ontario, Canada).

2.6. Probabilistic risk assessment

2.6.1. Lifetime average daily intake (LADI)

Exposure to cadmium following both inhalation and oral exposures (lifetime average daily intake, $LADI_i$ and $LADI_o$, respectively) were estimated using Eqs. (1) and (2), from USEPA (1989), modified for tobacco consumption:

$$LADI_i(\mu g/m^3) = \frac{C_i \times DTC_i \times ED \times EF}{DIR \times BW \times AT \times CF_i} \quad (1)$$

$$LADI_o(mg/kg-d) = \frac{C_o \times DTC_o \times ED \times EF \times CF_o}{BW \times AT} \quad (2)$$

where Ci is cadmium concentration (μg per cigarette) in machine-generated MSS; Co is cadmium concentration (μg per g dry weight) in SLT; DTCi (daily tobacco consumption) is cigarettes per day; DTCo is moisture adjusted g of SLT per day; ED is exposure duration (years); EF is exposure frequency (days per year); DIR is daily inhalation rate (L/kg-day); BW is body weight (kg); AT is averaging time (70 years × 365 days per year for ILCR calculation and ED × 365 - days per year for HQ calculations); CFi is a conversion factor of 10–3 m3/L; CFo is a conversion factor 10–6 mg/ng. LADI was calculated for each exposure route, inhalation in the case of cigarette smokers ($LADI_i$) and oral in the case of SLT consumers ($LADI_o$).

To account for variability in LADI values and to provide a more meaningful estimate of the probable range of exposures, a probabilistic approach using Monte Carlo simulation was incorporated to provide distributions around all exposure inputs. The simulation was run in Crystal Ball version 7.3.1 (Denver, Colorado, USA) with 10,000 iterations. Independent simulations at 1,000, 5,000, and 100,000 iterations were conducted to test the convergence and stability of the numerical output. The results showed that 10,000 iterations were sufficient to ensure the stability of the output distributions.

The variable distributions used included C, DTC, ED, EF, and BW. Parameter distributions, values, and sources are provided in Table 1. Distributions were fit using data from 34 cigarette brands for C_i (see Section 2.4) and 23 moist snuff and 7 chewing tobacco products for C_o (see Section 2.5) in combination with the distribution fitting function in Crystal Ball version 7.3.1. The C distributions were truncated at the minimum and maximum analytical data points. Goodness-of-fit tests provided by Crystal Ball included the Kolmogorov–Smirnov, Chi-Square, and Anderson–Darling. If the three tests were not in agreement, the Anderson–Darling test was preferred. DTC_o was constructed as an empirical distribution based on risk-maximizing SLT consumption assumptions of one to five cans or pouches per day, 34 g per can of moist snuff, and 85 g per pouch for chewing tobacco. DTC_i was constructed as an empirical distribution of daily cigarette consumption based on 1999–2006 NHANES (CDC, 2006). Distributions of EF and BW were also based on data from the 1999–2006 NHANES (CDC, 2006). EF was constructed as a discrete distribution with three possible values: 219, 292, and 365 days per year, corresponding to consumption of tobacco products for 3 days or less, 4 days, and 5 days out of the last 5 days, respectively. ED was based on US life expectancy data (Arias, 2006) and values were calculated as the sum of age (i.e., 18–100 years) and life expectancy subtracting 18 years, the minimum legal age for tobacco purchase in the US. ED and BW data

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Table 1
Probabilistic risk assessment parameter descriptions, distributions, values, and data sources.

Parameter	Designation	Units	Distribution/Value	Data source
Cadmium concentration	C	ng/g dry weight (SLT) ng/ cigarette (MSS)	SLT (moist snuff): Min Extreme (1283, 336) SLT (chewing tobacco): NORM(625.71,129.58) MSS: BETA(49185,5.20,1.98)	This study. See Methods for details.
Daily tobacco consumption	DTC	g/day, moisture adjusted[a] (SLT) cigarettes/day (MSS)	SLT (moist snuff): Empirical $\mu = 44.6$, min = 34, max = 170 SLT (chewing tobacco): Empirical $\mu = 133$, min = 85, max = 425 MSS: Empirical $\mu = 26.6$, P5 = 5.0, P95 = 70.0	1–5 cans or pouches per day; 34 g per can of moist snuff; 85 g per pouch of chewing tobacco 1999–2006 NHANES (CDC, 2006)
Exposure duration	ED	Years	UNIFORM(18,100) $\mu = 59.4$, P5 = 23, P95 = 96	ED = Age + LE-18
Age	Current age	Years	Discrete UNIFORM(18–100)	NA
LE	Life expectancy	Years	NA	US life tables (Arias, 2006)
Exposure frequency	EF	days/year	Empirical, $\mu = 319.6$	1999–2006 NHANES (CDC, 2006)
Body weight	BW	kg	Empirical, $\mu = 99$, P5 = 46, P95 = 157	1999–2006 NHANES (CDC, 2006)
Conversion factor	CF_o	mg/ng	10E-6	NA
Conversion factor	CF_i	m^3/L	10E-3	NA
Averaging time	AT	Days	70 × 365 (ILCR) ED × 365 (HQ)	USEPA (1989)
Daily inhalation rate	DIR	L/kg-d	GAMMA(193.99, 31.27, 2.46)	CalEPA (2003)
Inhalation unit risk	IUR	$(\mu g/m^3)^{-1}$	1.8E-3	USEPA (1992)
Minimal risk level, chronic	MRL	$\mu g/m^3$	1.0E-2	ATSDR (2008)
Reference dose	RfD	mg/kg-d	5.0E-4	USEPA (1994)

ATSDR = Agency for Toxic Substances and Disease Registry, CalEPA = California Environmental Protection Agency, HQ = hazard quotient, ILCR = incremental lifetime cancer risk, SLT = smokeless tobacco, MSS = cigarette mainstream smoke, NA = not applicable, NHANES = National Health and Nutrition Examination Survey, USEPA = United States Environmental Protection Agency.
See reference list for full source citations.
[a] Moisture: for moist snuff, mean (range) = 51.0 (31.9–56.3)%, for chewing tobacco, mean (range) = 23.9 (21.6–29.0)%.

were subsequently combined into a single bivariate distribution to ensure that age and BW were paired.

2.6.2. Cancer risk: incremental lifetime cancer risk (ILCR)

$ILCR_i$ was calculated by multiplying the $LADI_i$ (see Section 2.6.1) by the cancer inhalation unit risk (IUR, $(\mu g/m^3)^{-1}$) (Eq. (3)) (USEPA, 1989). Mean, 5th percentile, and 95th percentile for $ILCR_i$ were obtained from the outcome distribution.

$$ILCR_i = IUR \times LADI_i \quad (3)$$

The IUR of 1.8E-3 per $\mu g/m^3$ was derived by the USEPA (1992) based on an epidemiology study of males exposed to cadmium via inhalation in the workplace with subsequent deaths due to cancers of the lung, trachea, and bronchus (Thun et al., 1985). For cancer risk, a commonly referenced benchmark for the protection of public health used by the USEPA is an excess risk in the range of 10^{-6}–10^{-4} (i.e., the probability of 1 in 1,000,000 to 1 in 10,000 that an individual may develop cancer when exposed to a carcinogen for a lifetime).

2.6.3. Non-cancer hazard: Hazard quotient (HQ)

Non-cancer hazards (hazard quotient, HQ) were assessed by comparing the average daily intake from inhalation exposure (ADI_i) with the chronic minimal risk level (MRL, $\mu g/m^3$) (ATSDR, 2008) for inhalation exposure (Eq. (4)) and comparing the average daily intake from oral exposure (ADI_o) with the reference dose (RfD, mg/kg-d) (USEPA, 1994) for oral exposure (Eq. (5)) (USEPA, 1989). For HQ_o, the moist snuff and chewing tobacco HQs were combined into one HQ weighted by the number of products included in each category. Mean, 5th percentile, and 95th percentile for HQs were obtained from the outcome distributions.

$$HQ_i = \frac{ADI_i}{MRL} \quad (4)$$

$$HQ_o = \frac{ADI_o}{RfD} \quad (5)$$

MRL and RfD values represent an exposure level below which adverse effects would not be expected to occur following chronic exposure. These toxicity values incorporate margin of safety factors to account for variability in human response (i.e., sensitive sub-populations). The RfD of 5.0E-4 mg/kg-day (USEPA, 1994) was derived by USEPA based on human studies of chronic cadmium exposures with "significant proteinuria" (USEPA, 1994) as the endpoint. The chronic duration inhalation MRL of 0.01 $\mu g/m^3$ was derived by ATSDR (2008) using environmental epidemiology studies and urinary cadmium concentration estimates associated with excess risk of proteinuria. HQ is not a direct measure of risk of non-cancer health effects, but rather a ratio of actual exposure to an established threshold exposure value. If the actual cadmium exposure (i.e., the ADI) is lower than the corresponding threshold exposure (e.g., RfD), the HQ < 1 and the hazard is not expected to be a threat to public health. If the cadmium exposure exceeds the corresponding threshold exposure (i.e., HQ > 1), potential non-cancer effects may exist (USEPA, 1989).

3. Results

3.1. Epidemiology data – Cadmium exposure

Evaluation of available epidemiological data showed that some health effects associated with occupational and/or environmental cadmium exposure may also be associated with tobacco consumption. It is well-accepted that cadmium exposures in humans are associated with kidney, bone, and non-cancer respiratory disease; it is generally accepted that cadmium exposure via inhalation is associated with lung cancer in humans. Although epidemiological evidence is not conclusive, some studies have associated cadmium exposure with cardiovascular disease and pancreatic cancer. Because these are health outcomes of potential concern with SLT consumption (see Section 3.3), they were included in this analysis. The lowest U–Cd or B–Cd concentrations identified in the scientific literature to be associated with each of these adverse outcomes is presented in Table 2. Of all outcomes, the lowest effect level identified was a U–Cd level of 0.6 µg per g creatinine associated with decreased bone mineral density in women following environmental exposures (Schutte et al., 2008).

Table 2
Lowest identified cadmium biological concentrations associated with adverse health effects in humans (ATSDR, 2008).

	Cadmium concentration	Source citation
Lung cancer	1 μg/g creatinine	Nawrot et al., 2006
Decreased respiratory function	4 μg/g creatinine	Cortona et al., 1992
Decreased bone mineral density	0.6 μg/g creatinine	Schutte et al., 2008
Kidney damage (increased pHC)	1 μg/g creatinine	Järup et al., 2000
Myocardial infarction	0.88 μg/g creatinine	Everett and Frithsen, 2008
Pancreatic cancer	11.1 ng/mL serum	Kriegel et al., 2006

pHC = human complex forming glycoprotein (α1-microglobulin).
See reference list for full source citations.

3.2. Epidemiology data – Cigarette smoking

Of the human health effects associated with cadmium exposure, it is generally accepted that cigarette smoking is associated with increased risk of non-cancer respiratory disease, lung cancer, cardiovascular disease, and pancreatic cancer (USDHHS, 2004). Cigarette smoking is also associated with decreased bone mineral density in post-menopausal women (USDHHS, 2004), and nephropathy in individuals with diabetes (USDHHS, 2010).

3.3. Epidemiology data – SLT consumption

For SLT consumers, IARC has determined that there is sufficient evidence that SLT causes pancreatic cancer (IARC, 2007). The American Heart Association has stated that there is evidence that long-term SLT consumption may be associated with increased risk of cardiovascular mortality, specifically myocardial infarction and stroke (Piano et al., 2010).

3.4. Biomonitoring data

Results from the current analysis of B–Cd and U–Cd data from the 1999–2006 NHANES showed that mean B–Cd and U–Cd concentrations were higher in cigarette smokers than in SLT consumers, and B–Cd and U–Cd in SLT consumers were not significantly different than in non-consumers of tobacco (Table 3, Fig. 1A, 1B and 2A, 2B). Additionally from the analysis of 1999–2006 NHANES data, serum cotinine was statistically significantly associated with both U–Cd and B–Cd for cigarette smokers, and increasing serum cotinine was associated with increased U–Cd and B–Cd (Fig. 2A and Fig. 2B). This statistical relationship between cotinine and cadmium was not observed for SLT consumers and non-consumers of tobacco (Fig. 2A and Fig. 2B).

On average, the U–Cd and B–Cd concentrations in tobacco users in NHANES 1999–2006 (Table 3) were less than the lowest biological cadmium concentrations identified from previously published epidemiology studies to be associated with adverse health outcomes (Table 2).

Table 3
Biomarkers of cadmium exposure by tobacco consumption category, geometric mean (NHANES 1999–2006).

Cigarette smokers	Unadjusted	Adjusted[a]
U–Cd (μg/g creatinine) (n = 1180)	0.39	0.44
B–Cd (ng/mL) (n = 3679)	0.89	0.95
Smokeless tobacco consumers	Unadjusted	Adjusted[a]
U–Cd (μg/g creatinine) (n = 87)	0.16	0.25
B–Cd (ng/mL) (n = 272)	0.29	0.39
Non-consumers of tobacco	Unadjusted	Adjusted[a]
U–Cd (μg/g creatinine) (n = 4110)	0.24	0.25
B–Cd (ng/mL) (n = 12454)	0.31	0.31

[a] Adjusted for age, gender, race/ethnicity, body mass index, survey year, and tobacco consumption category. B–Cd = blood cadmium, U–Cd = urine cadmium.

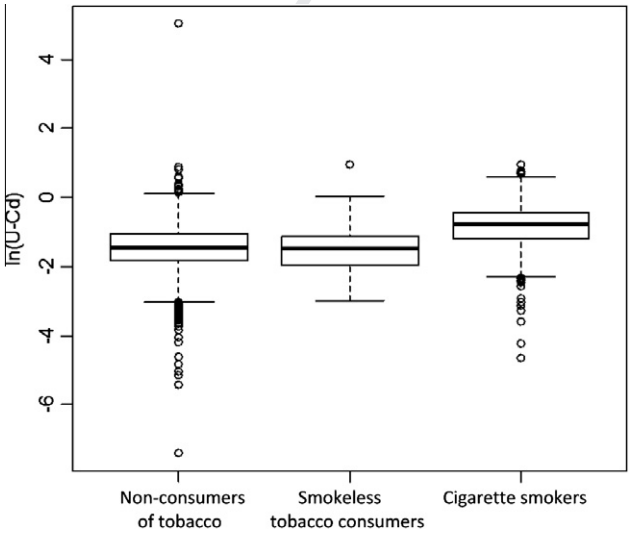

Fig. 1A. U–Cd (μg/L) concentrations by tobacco consumption category (NHANES 1999–2006). U–Cd = urinary cadmium; SLT = smokeless tobacco. Cigarette smokers, n = 1180; SLT consumers, n = 87; Non-consumers, n = 4110. Adjusted for age, gender, race/ethnicity, body mass index, urinary creatinine, survey year, and tobacco consumption category. Cigarette smokers adjusted for a log cotinine value of 4.83 ng/mL (125.21 ng/mL on raw scale), the geometric mean for all cigarette smokers evaluated.

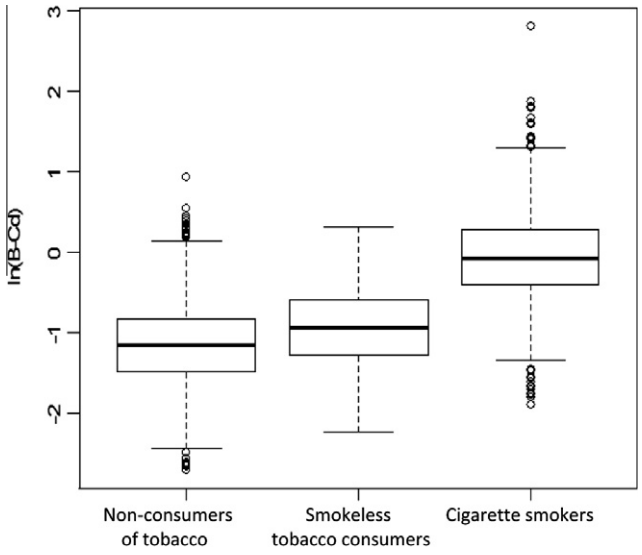

Fig. 1B. B–Cd (ng/mL) concentrations by tobacco consumption category (NHANES 1999–2006). B–Cd = blood cadmium; SLT = smokeless tobacco. Cigarette smokers, n = 3679; SLT consumers, n = 272; Non-consumers, n = 12454. Adjusted for age, gender, race/ethnicity, body mass index, survey year, and tobacco consumption category. Cigarette smokers adjusted for a log cotinine value of 4.83 ng/mL (125.21 ng/mL on raw scale), the geometric mean for all cigarette smokers evaluated.

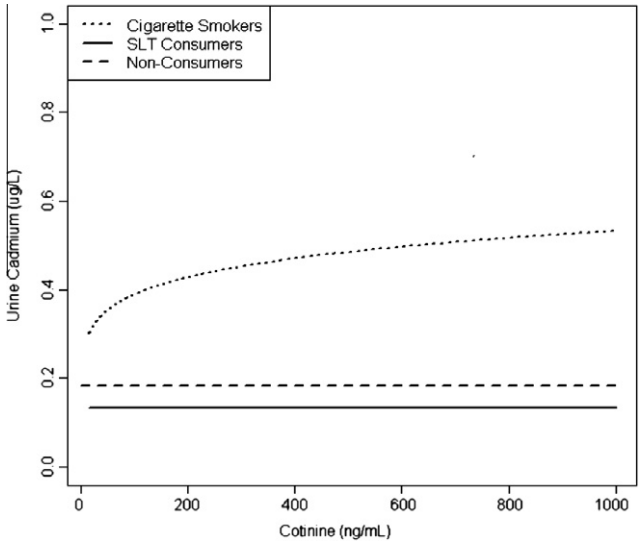

Fig. 2A. Regression of serum cotinine and U–Cd (NHANES 1999–2006). SLT = smokeless tobacco; Non-consumers = non-consumers of tobacco. Cigarette smokers, $n = 1180$; SLT consumers, $n = 87$; Non-consumers, $n = 4110$. See methods for details. For graphing, model parameters were fixed as follows: age = 39–49 (category), sex = male, race = White, non-Hispanic, BMI = 22.7–26.1 (category), creatinine = log 4.74.

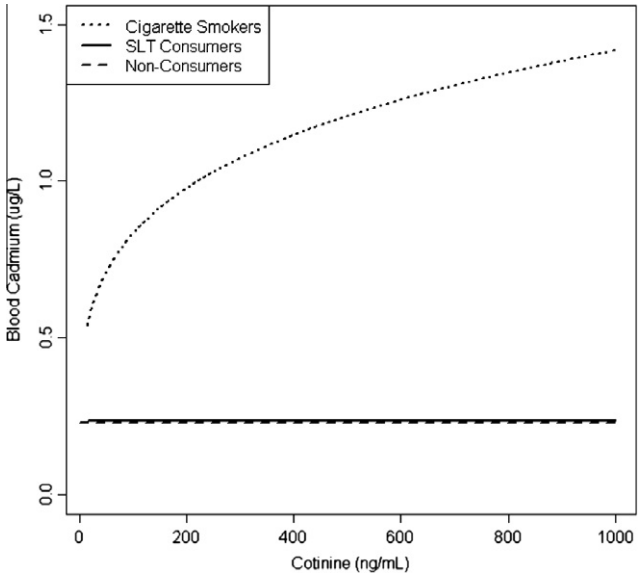

Fig. 2B. Regression of serum cotinine and B–Cd (NHANES 1999–2006). SLT = smokeless tobacco; Non-consumers = non-consumers of tobacco. Cigarette Smokers, n = 3679; SLT consumers, $n = 272$; Non-consumers, $n = 12454$. See methods for details. For graphing, model parameters were fixed as follows: age = 39–49 (category), sex = male, race = White, non-Hispanic, BMI = 22.7–26.1 (category).

3.5. Comparison of NHANES U–Cd and B–Cd levels with Biomonitoring Equivalents (BEs)

Comparison of 1999–2006 NHANES U–Cd values from the current analysis with the previously established urine BE of 1.5 μg/L (Hays et al., 2008a) indicated that <10% of smokers,<5% of SLT consumers, and <2% of non-consumers of tobacco exceeded the urine BE value (Fig. 3A). These percents were statistically significantly different among the three groups. B–Cd levels from 1999–2006 NHANES participants from the current analysis exceeded the previously established blood BE of 1.7 μg/L (Hays et al., 2008a) in approximately 18% of cigarette smokers and <1% of both SLT consumers and non-consumers of tobacco (Fig. 3B). For B–Cd, the percent of SLT consumers and non-consumers of tobacco that exceeded the BE were not statistically significantly different from each other, but were both statistically significantly different from the 18% of cigarette smokers exceeding the BE.

3.6. Cadmium concentrations in cigarette MSS and SLT products

The mean cadmium concentration in MSS of the cigarettes analyzed was 136 ng per cigarette, with a range of 49–185 ng per cigarette. The mean cadmium content of the SLT (moist snuff and chewing tobacco) products evaluated was 1,028 ng per g dry weight tobacco with a range of 469–1,871 ng per g dry weight. The cadmium concentrations detected in cigarette MSS and SLT products in this analysis were consistent with previously reported concentrations (Counts et al., 2005; Hoffmann et al., 1987; Maier et al., 1989; Pappas et al., 2008).

3.7. Probabilistic risk assessment

Mean, 5th percentile, and 95th percentile $ILCR_i$, HQ_o, and HQ_i values are presented in Table 4. The mean HQ_o of 0.68 and the mean HQ_i of 12.98 indicate that mean non-cancer hazard estimates fall below US regulatory guidelines (i.e., HQ < 1, USEPA, 1989) for SLT consumers, but not for cigarette smokers. The mean calculated $ILCR_i$ for cadmium exposure in cigarette smokers was 2.5E-4, approximately 2.5× greater than the upper limit of a commonly referenced benchmark range for the protection of public health (i.e., 10^{-6}–10^{-4}). Because cadmium is not considered to be carcinogenic via oral exposures, no oral ILCR was calculated (ATSDR, 2008; USEPA, 1992).

4. Discussion

Cadmium was detected in cigarette MSS, SLT products, and in the blood and urine of both tobacco consumers and non-consumers of tobacco (Fig. 1A, Fig. 1B, Fig. 2A, Fig. 2B and Table 3). Among SLT consumers, cadmium was detected in blood and urine at levels not statistically significantly different from concentrations measured in non-consumers of tobacco, whereas mean B–Cd and U–Cd concentrations in cigarette smokers were statistically significantly increased compared with both SLT consumers and non-consumers of tobacco. U–Cd values from this analysis (Table 3) are consistent with previously published U–Cd values for smokers and non-smokers based on NHANES data (Mortensen et al., 2011; Tellez-Plaza et al., 2012). Consistent with increased cadmium biomarkers detected in cigarette smokers compared with SLT consumers, pulmonary absorption of cadmium (e.g., cadmium fumes, MSS) has been reported to be approximately 25% to 50%, while absorption from the gastrointestinal tract has been estimated to range between 0.5% and 12% (Järup and Akesson, 2009; Hays et al., 2008a). The statistical relationship observed between serum cotinine and U–Cd and B–Cd in cigarette smokers (Fig. 2A and Fig. 2B), but not in SLT consumers, provides additional support that cadmium exposure in SLT consumers may not be related to tobacco consumption. Of note, this pattern was not different in SLT consumers and non-consumers of tobacco (Fig. 2A and Fig. 2B). Results from previous studies have indicated U–Cd and B–Cd concentrations are higher in cigarette smokers than in non-smokers and SLT consumers, and that increasing B–Cd and U–Cd in cigarette smokers are associated with increasing serum or urine cotinine concentrations (Naufal et al., 2011; Shaham et al., 1996; Willers et al., 1992).

In comparison with previously published epidemiology studies, mean U–Cd and B–Cd levels in cigarette smokers and SLT consum-

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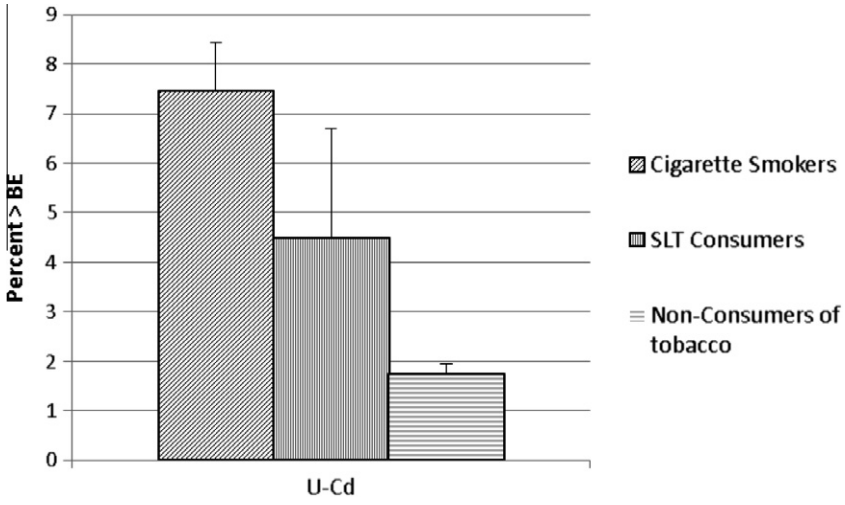

Fig. 3A. Percent of NHANES (1999–2006) participants with U–Cd > BE. U–Cd = urinary cadmium; SLT = smokeless tobacco; BE = biomonitoring equivalent, i.e., the concentration of a chemical in blood or urine that is consistent with an existing health-based exposure guideline. U–Cd BE = 1.5 μg/L. (Hays et al., 2008a) Error bars represent standard error of the mean. Cigarette smokers, $n = 1180$; SLT Consumers, $n = 87$; Non-consumers, $n = 4110$.

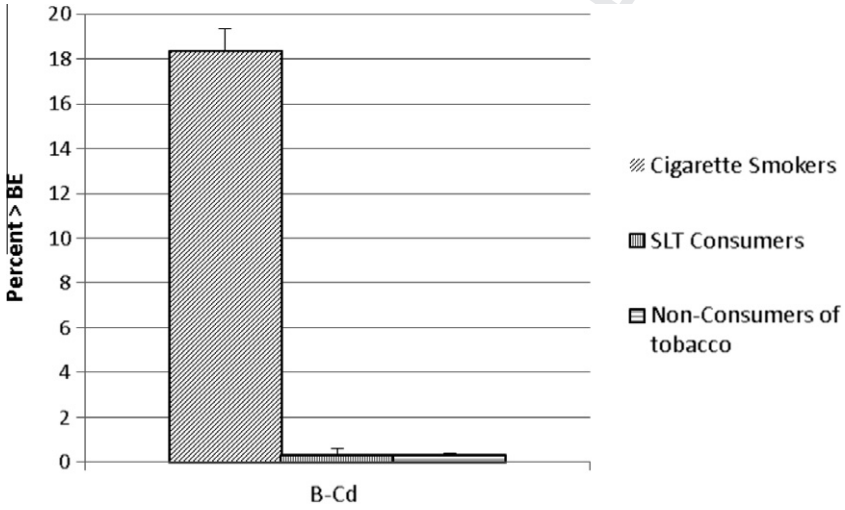

Fig. 3B. Percent of NHANES (1999–2006) participants with B–Cd > BE. B–Cd = blood cadmium; SLT = smokeless tobacco; BE = biomonitoring equivalent, i.e., the concentration of a chemical in blood or urine that is consistent with an existing health-based exposure guideline. B–Cd BE = 1.7 μg/L. (Hays et al., 2008a) Error bars represent standard error of the mean. Cigarette Smokers, $n = 3679$; SLT Consumers, $n = 272$; Non-Consumers, $n = 12454$.

Table 4
Calculated incremental lifetime cancer risk ($ILCR_i$) and hazard quotient (HQ_o, HQ_i) values for cadmium from cigarette smoking (inhalation) and SLT consumption (oral).

	5th percentile	Mean	95th percentile
Cancer risk, inhalation ($ILCR_i$)	3.9E-5	2.5E-4	6.60E-4
Non-cancer hazard, inhalation (HQ_i)	1.98	12.98	35.24
Non-cancer hazard, oral (HQ_o)	0.21	0.68	1.87

HQ_i = hazard quotient, inhalation; HQ_o = hazard quotient, oral; $ILCR_i$ = incremental lifetime cancer risk, inhalation; SLT = smokeless tobacco.

ers in this analysis (Table 3) were lower than the lowest concentration of U–Cd observed in environmentally and occupationally exposed populations affected by cadmium exposure (Table 2). For example, of the well-established associations between cadmium exposure and adverse effects, lowered respiratory function has been associated with U–Cd concentrations of 4 μg per g creatinine (Cortona et al., 1992), a concentration 16-fold higher than the mean U–Cd for 1999–2006 NHANES SLT consumers (0.25 μg per g creatinine) and approximately 10-fold higher than the mean U–Cd for 1999–2006 NHANES cigarette smokers (0.44 μg per g creatinine) from this analysis. Adverse bone effects are also a well-established adverse outcome independently associated with cadmium exposure at a lowest identified cadmium concentration of 0.6 μg per g creatinine (Schutte et al., 2008). The mean U–Cd concentrations in 1999–2006 NHANES SLT consumers in this analysis were more than 50% lower and the mean U–Cd concentrations in

1999–2006 NHANES cigarette smokers were more than 25% lower. Overall, the results from the analysis of biomonitoring data indicated that mean U–Cd and B–Cd levels in NHANES SLT consumers and cigarette smokers were lower than the lowest cadmium concentrations identified from epidemiology studies to be independently associated with adverse health effects, although some NHANES tobacco consumers did exceed these values. It should be noted that detectable adverse health effects in some previously published epidemiology studies may have been limited by sample size and/or duration of follow-up.

Additional evidence that the majority of tobacco consumers, and SLT consumers in particular, are not exposed to cadmium at levels expected to be of concern was provided in the comparison of biomonitoring data with established BE values. As noted, mean U–Cd concentrations did not exceed the cadmium urine BE value in the majority of cigarette smokers (93%) and SLT consumers (96%) (and 98% of non-consumers), with U–Cd concentrations most representative of the cadmium dose metric of the critical toxic response (i.e., renal cortex cadmium concentration). These values are consistent with results from a previous analysis of U–Cd data from NHANES 1999–2006, which indicated approximately 10% of smokers and 2% on non-smokers (excluding individuals with chronic kidney disease) had U–Cd levels that exceeded 1 μg/g creatinine (Mortensen et al., 2011). B–Cd concentrations, representative of recent cadmium exposure, did not exceed the blood BE in approximately 82% of cigarette smokers and nearly 100% of SLT consumers.

As noted, an HQ < 1 indicates the non-cancer hazard is not expected to be a threat to public health, including sensitive subgroups. The PRA in this analysis predicted low potential for adverse non-cancer effects in SLT consumers ($HQ_o = 0.68$), although this was not observed for cigarette smokers ($HQ_i = 12.98$) in this analysis. Because cadmium is not considered to be carcinogenic via the oral route, no cancer risk from oral exposure was estimated (ATSDR, 2008; USEPA, 1992). Cadmium is, however, generally considered to be carcinogenic to humans following inhalation exposures, and results of the ILCR calculation for cadmium in MSS indicated that the risk was approximately 2.5× greater than the generally accepted excess lifetime cancer risk upper limit of 1 in 10,000. This $ILCR_i$ estimate assumed complete absorption of cadmium (a risk-maximizing assumption, generally accepted in risk assessment) and incorporated cadmium yields from machine generated smoking at an intense smoking regimen. Machine-generated smoke yields do not represent actual smoker exposures and an intense smoking regimen likely overestimates true exposure (Borgerding and Klus, 2005). Additionally, as previously noted, if only 25% to 50% of cadmium inhaled from cigarette smoking is bioavailable in the lung, it is possible that the cancer risk estimate would be reduced to within the range of the generally accepted upper limit value of 1 in 10,000. The $ILCR_i$ estimate calculated in this analysis was within the range of a previous estimate of 1 to 18 lung cancers per 10,000 due to the cadmium in cigarette smoke, which was based on epidemiology data (Hertz-Picciotto and Hu, 1994).

Strengths of this evaluation include the use of data from NHANES, a well-established biomonitoring program in the US. NHANES data provide a large sample, designed to be representative of the US population. Individual level data are available, which are useful for comparison across tobacco consumption categories (i.e., cigarette smokers, SLT consumers, and non-consumers of tobacco). NHANES data may, however, be subject to sampling and non-sampling error. Laboratory data may be subject to measurement variation, and tobacco consumption data are based on self-report by survey participants and may be subject to recall bias and/or misunderstanding. This analysis, however, minimized some tobacco category misclassification by confirming non-consumers of tobacco using a serum cotinine cut-off value, and participants reported consumption under actual conditions of use (as opposed to experimental conditions). Similar to the US population, tobacco consumers are a fraction of NHANES participants, and of tobacco consumers, the majority is cigarette smokers. Snuff and chewing tobacco categories were combined due to small sample sizes, recognizing that differences in these SLT product categories exist (e.g., in product composition). It is also worth noting that it is possible that tobacco products marketed and tested in 2006 may not be the same as those used by NHANES participants in prior years (e.g., 1999–2000). However, the cadmium concentrations detected in cigarette MSS and SLT products in this analysis were consistent with previously reported concentrations (Counts et al., 2005; Hoffmann et al., 1987; Maier et al., 1989; Pappas et al., 2008).

Reducing the levels of known toxicants in tobacco and/or reducing human exposures to known toxicants from the consumption of tobacco products may be relevant to the discussion of risk modification of tobacco products (FSPTCA, 2009). The results of this analysis of NHANES biomonitoring data indicated that cadmium exposures in SLT consumers were significantly lower than exposures in cigarette smokers and not different than cadmium exposures in non-consumers of tobacco. Whereas U–Cd and B–Cd were associated with urine cotinine in these cigarette smokers, the same association was not observed in the SLT consumers, indicating cadmium exposure in SLT consumers is likely not related to tobacco exposure. Additionally, cadmium exposures in most tobacco consumers in this population were below the health-based exposure guideline for cadmium (i.e., BEs) and the biological concentrations of cadmium (i.e., U–Cd and B–Cd) in most tobacco consumers were lower than cadmium concentrations associated with adverse health effects in previously published epidemiology studies. Results of these comparisons suggest that cadmium may not be independently associated with adverse health outcomes in tobacco consumers, although the potential role of toxicological interactions between cadmium and other tobacco constituents are unknown (and beyond the scope of this evaluation). PRA results indicated differences in hazard by tobacco category, and results for SLT consumers were within generally accepted regulatory guidelines. It is not clear whether any one constituent in tobacco has a direct and independent effect on the development of tobacco consumption associated adverse health effects, but the evidence presented here suggests that it is possible that cadmium may not independently contribute to adverse health outcomes in tobacco consumers. Additionally, these results confirm that, in terms of exposure and risk profiles, cigarettes and SLT products are not the same.

5. Conflict of interest statement

The authors declare that there are no conflicts of interest.

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